

Metallic Elements in Fossil Fuel Combustion Products: Amounts and Form of Emissions and Evaluation of Carcinogenicity and Mutagenicity

by Velimir B. Vouk* and Warren T. Piver*

Metallic elements contained in coal, oil and gasoline are mobilized by combustion processes and may be emitted into the atmosphere, mainly as components of submicron particles. The information about the amounts, composition and form of metal compounds is reviewed for some fuels and combustion processes. Since metal compounds are always contained in urban air pollutants, they have to be considered whenever an evaluation of biological impact of air pollutants is made.

The value of currently used bioassays for the evaluation of the role of trace metal compounds, either as major biologically active components or as modifiers of biological effects of organic compounds is assessed. The whole animal bioassays for carcinogenicity do not seem to be an appropriate approach. They are costly, time-consuming and not easily amenable to the testing of complex mixtures. Some problems related to the application and interpretation of short-term bioassays are considered, and the usefulness of such bioassays for the evaluation of trace metal components contained in complex air pollution mixtures is examined.

Introduction

Of some 80 elements that are considered as metals, about 50 have been reported to be present in coal (1-5), 35 in crude oil (6-13), 30 in fuel oil (8, 14) and about 20 in gasoline (6, 15). As a result of combustion, these elements are mobilized and may be emitted into the atmosphere primarily as constituents of particulate matter containing a mixture of inorganic and organic substances (16), the composition and structure of particulate emissions depending on the fuel and the combustion process used. Human exposure to atmospheric particulates is combined with exposure to gaseous emissions such as sulfur dioxide, oxides of nitrogen and carbon monoxide. Unless bound to organic ligands, the only metallic or metallike elements that may be emitted in gaseous discharges in measurable con-

centrations are mercury and selenium (17). Since metallic elements and their compounds are always present in airborne particulates, they have to be considered in any evaluation of mutagenicity and carcinogenicity of air pollutants arising from fossil fuel combustion.

Besides being air contaminants possibly hazardous to human health, some metallic elements can act as catalysts in atmospheric transformations of primary air pollutants into secondary products, and can cause economic loss due to corrosion and abrasion of materials and surfaces. In addition they may affect vegetation and animal life.

Direct human exposure to metallic elements from air pollution takes place by inhalation and ingestion of inhaled particles. Polluted air may increase the concentrations of metallic elements in soil, water and food and thus add to the human exposure to metallic elements from these sources. However, ambient air pollution is generally a minor contributor to the total human exposure to metals and metal compounds, except in the immediate vicinity of

National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC.

sources of emission, or when the fossil fuel contains a particularly large amount of an element as does the coal from a region in Czechoslovakia, in which arsenic concentration amounts to about 900–1500 mg/kg dry substance (18) compared to an average of 14 mg/kg in the U.S. coal (19).

Although the concentrations of metallic elements in polluted urban air are usually small, for some metals the total amount emitted by the combustion of fossil fuels, particularly coal, may be of the same order of magnitude or larger than the total worldwide industrial production. A good example is germanium. As estimated by Paone (20), about 2000 metric tons of germanium are discharged in stack gases, flue dust and ashes from coal burning plants in the United Kingdom whereas the total world production is of the order of 100 tons per year (21). Other examples are arsenic, cadmium, selenium, and vanadium (22).

In the present paper we are concerned with metallic elements emitted into the air as a result of fossil fuel combustion, and with the chemical and physical form in which they are discharged. No attempt has been made to estimate human exposures because they depend to a large extent on the proximity of emission sources and other local conditions. The existing laboratory data on mutagenicity and carcinogenicity of metallic elements contained in air pollution from fossil fuel combustion are summarized, and the applicability to metal contaminants in air of currently used laboratory methods for the evaluation of mutagenicity and carcinogenicity is briefly discussed.

It may be useful to define some basic concepts that will be often used during discussions at this meeting. The first two concepts that require definition are "risk" and "hazard." The term risk means the probability that an individual or a group of individuals will incur a deleterious effect as a result of an exposure to a given environmental agent. This definition is very similar to the internationally accepted definition of risk in radiological protection (23) or to the definition proposed by the Preparatory Committee of the United Nations Conference on the Human Environment (24). In toxicology, risk assessment refers to a process by which toxicological information is reviewed to determine whether or not a chemical may cause certain adverse effects and, if so, at what levels of exposure or dose, and with what probability (expected frequency). Hazard assessment is concerned with the evaluation of the health impact of a chemical under actual conditions of exposure (25). Thus, the validity of health hazard assessment depends both on how adequate is the available information on toxicity and risk, and how appropriate and reliable

is the estimate of the level and quality of exposure.

The concept of exposure also requires clarification. According to a UNEP/WHO report (26), the exposure to a given pollutant is a measure of the contact between the pollutant and the outer or inner surface (e.g., alveolar surface or gut) of the human body. It is usually expressed in terms of concentration of the pollutant in the medium (e.g., ambient air and food) interfacing with body surfaces. Once absorbed, the pollutant gives rise to doses in various organs and tissues. Doses are measured in terms of concentration in the tissues. Records of exposure and dose should include an indication of the time and frequency at which an individual is subjected to them. In addition to the concentration and time of contact, quantitative evaluation of exposure involves estimation of the relative contribution to the total exposure of different pathways — inhalation, ingestion and skin contact. Qualitative assessment of exposure requires the knowledge of the chemical form and physical properties (e.g., solubility, particle size) of the substance considered and of other substances to which the body is exposed at the same time, or somewhat earlier or later. This last question is usually difficult to answer, although it is very important because biological effects depend on interactions that may result from the presence of several substances during exposure (27).

For many chemicals, information on toxicity is available only for experimental animals. Assessment of human health risk from such information involves many uncertainties, the major ones being the quality and biological appropriateness of laboratory animal experiments. It should be also pointed out that the evaluation of one particular toxicity, e.g., carcinogenicity, should take into account other forms of biological activity of the substance under consideration, particularly the possible adverse effects on different organs and systems such as the liver, kidney and hemopoietic and immune systems, because such effects may influence the particular form of toxicity which is being evaluated.

One characteristic of metallic elements (and, of course, all other elements) is that they are not biodegraded. Once absorbed, a metallic element remains in the organism until it is excreted. However, its chemical form and the oxidation state, and thus its toxicity, may change as a result of chemical or biochemical transformations.

The concept of dose commitment, originally developed for radioactive substances has been found useful for pollutants such as lead, cadmium and arsenic (28). Similarly, the radiological concept of collective dose has found application in the toxicology of metallic elements (29, 30).

Trace Elements in Fossil Fuels

The metallic element content of different fossil fuels varies considerably both in number of elements and their concentration range. A comparison

of the average content of some metallic elements (listed by increasing atomic number) in principal fossil fuels is given in Table 1. The values for coal have been taken from papers by Edwards et al. (2), Gluskoter (4), Nicholls (3), Rao and Gluskoter (5),

Table 1. Concentrations of some metallic elements in fossil fuels.

Element	Concentration, ppm				
	Coal ^a	Crude oil ^b	Residual fuel oil ^c	Gasoline ^d	Earth's crust ^e
Li	65	0.5-1.5	0.03		65
Be	3-25	0.002	0.0004	< 0.001	6
Mg	2,000	1-2.5	2.1	0.003	21,000
Al	10,000	1.0	0.5	0.01	88,200
Sc	5	0.001	0.001		5
Ti	500	0.3	0.1		6,300
V	25	47	82	0.0015	100
Cr	10	0.1	1.3	0.017	200
Mn	50	1.4	0.4	0.016	930
Fe	10,000	41	14.0	1.07	51,000
Co	5-25	1.7	0.2		40
Ni	15	32.3	55	0.086	100
Cu	15	1.3	0.45	0.14	100
Zn	50	30	1.23	0.16	40
Ga	7	0.35	0.01		15
Ge	5-45	0.002	0.001		7
As	5-45	0.26	0.42	0.0015	5
Se	3	0.53	0.07	< 0.06	0.6
Rb	100				310
Sr	500	0.0001-0.1	0.4		420
Y	10	0.0001-0.27	0.001		31
Zr	70	0.0004-0.35			190
Mo	5	0.031	10		15
Ag	0.5	0.00001-0.004	0.0001	0.015	0.1
Cd	0.5	0.01	0.01	0.015	0.5
Sn	2-20	0.1-0.3	0.01		40
Sb	1.4	0.58	0.12	0.025	1
Ba	500	0.34	3.0		390
La	10	0.001-0.42	0.005		19
Ce	11.5-17	0.003-0.07	0.01		44
Pr	2.2				5.6
Nd	4.7	0.004-0.15			24
Sm	1.6				6.5
Eu	0.7	0.05			1.0
Gd	1.6				6.3
Tb	0.3				1.0
Ho	0.3				1.2
Er	0.6	0.003	0.001		2.4
Tm	0.1				0.3
Yb	0.5				2.6
Lu	0.07-4				0.7
Ta	<1				
W	20				69
Re	0.05				0.001
Hg	0.012-0.15	3.24	10		0.5
Tl					0.3
Pb	25	0.24	2.3	400	16
Bi	5.5				0.2
Th					11
U	1.0	0.06	0.001		4

^aCoal data from Ruch et al. (1), Edwards et al. (2), Nicholls (3), Gluskoter (4), and Rao and Gluskoter (5).

^bCrude oil data from Shah et al. (6, 7), Williams and Cawley (8), American Petroleum Institute (9) and Jones (31).

^cFuel oil data from Bertine and Goldberg (14), Lee and von Lehmden (32) and American Petroleum Institute (9).

^dGasoline data are an average of the trace element contents for regular, premium, and low-lead gasoline grades and are taken from Jungers et al. (15).

^eAbundance of elements in the earth's crust data from Goldschmidt (33).

and Ruch et al. (1). Data for crude oil and petroleum distillate fuels have been compiled from a publications of the American Petroleum Institute (9), and from Bertine and Goldberg (14), Jones (31), Jungers et al. (15), Lee and von Lehmden (32), Shah et al. (6, 7) and Williams and Cawley (8). The last column in Table 1 lists average crustal concentrations of 50 metallic elements (33).

By far the greatest number and, with rare exceptions, the highest concentrations of metallic elements are found in coal. Average metallic element contents for crude oil (petroleum) and two of its principal refined products, residual fuel oils and gasoline, are listed in separate columns. Vanadium, nickel and zinc are found in higher concentrations in the higher boiling point, heavier residual oil fractions than in the lower boiling point, lighter fractions used for gasoline. The lead content is much higher in gasoline than in crude oil or fuel oil because it is added as alkyllead after the refining process. The last column in Table 1, containing crustal concentrations of metallic elements, has been included to draw attention to the close similarity between the content of metallic elements in earth's crust and their content in coal.

Combustion of fossil fuels in electric power plants, commercial boilers and furnaces used for space heating, and in motor vehicle engines is the principal man-made source of metallic elements in the atmosphere. There are many factors that determine which elements enter the atmosphere, and to what extent. The more important of these factors include the design and operating conditions of the combustion chamber (such as its temperature) and the associated air pollution control equipment, the chemical form of the element in the fuel, and the volatility of the element or compound. All these factors have to be considered when trying to predict the composition of combustion products emitted into the atmosphere because the mere presence of a metal in the fuel does not necessarily indicate that it will be emitted as an air pollutant.

Emissions from Gasoline Combustion

Both the gaseous and particulate matter emission profiles of the four-stroke, spark-ignited internal combustion engine have been studied extensively. This particular engine is still the most commonly used power supply for passenger vehicles, buses and trucks. Diesel engines and rotary engines have not achieved the same level of popularity.

The regulated gaseous exhaust emissions from automobiles in the United States are carbon monox-

ide, oxides of nitrogen, and unburnt hydrocarbons. Since 1975, emission control devices have been used to control the emissions of carbon monoxide and hydrocarbons by oxidizing these compounds to carbon dioxide and water. These devices have been very successful in reducing the emissions of carbon monoxide and hydrocarbons by as much as 95% of their uncontrolled levels, but they have no effect on nitrogen oxide emissions. A reduction catalyst, which would precede the oxidation catalyst, has been proposed to reduce nitrogen oxide emissions but it is still in development. All grades of gasoline however, contain a small residual amount of sulfur (15), and the oxidation catalysts are very effective in oxidizing sulfur dioxide formed during fuel combustion to sulfur trioxide. As a result, the emission of sulfuric acid mist from vehicles which are equipped with these devices has considerably increased. Because this mist is emitted near ground level, the potential for human exposure is very high. The use of low sulfur gasoline, however, has greatly reduced this emission.

Lead is a poison for oxidation catalysts and the content of alkyllead antiknock agents had to be greatly reduced (34). Unleaded gasolines have an average lead content of 0.03 g Pb/gal (8 mg/L). Average lead content of other grades of gasoline is much higher and ranges from 0.5 g Pb/gal (134 mg/L) for low lead gasolines, through 1.86 g Pb/gal (494 mg/L) for regular grades to 2.3 g Pb/gal (600 mg/L) for premium grades (15). More recent sales records for gasoline lead additives are not available, but the use of lead additives in the United States had declined significantly from 242,000 tons (220 metric kilotons) in 1970 to 150,000 tons (136 metric kilotons) in 1975 (35). The worldwide consumption of lead fuel additives for the same period did not decline so rapidly and was listed as 274,000 tons (250 metric kilotons) in 1975 (36). The consumption of lead fuel additives in Europe actually remained fairly constant at about 82,000 tons (75 metric kilotons) for the same time interval (36).

Lead in exhaust emissions from uncontrolled spark ignited engines is commonly present in particles of submicron size, and in complex aggregates together with carbonaceous material and a variety of organic compounds such as polycyclic aromatic hydrocarbons. In terms of number concentration, most particles are smaller than 0.5 μm (37-44), irrespective of different driving conditions and engine types, and spheroidal in shape. Lead is preferentially deposited on the surface of these particles (45), and its chemical form is most probably a mixed halide, PbBrCl , because halide scavengers are added to remove lead deposits from the surface of the combustion chamber (38, 44).

Several options have been used to replace the antiknock properties of alkyllead compounds. One option is to use gasoline to which aromatic compounds such as benzene, toluene and xylenes have been added in greater amounts. Another option is to replace lead with a manganese fuel additive such as methylcyclopentadienylmanganese tricarbonyl (MMT), that has similar antiknock and octane number-boosting properties. Studies with this manganese fuel additive at the recommended use level of 0.125 g Mn/gal (33 mg/L) gave exhaust emission particles with mass median diameter of 0.2–0.4 μm (46). Manganese was emitted as MnO , Mn_2O_3 (46, 47).

Emissions from Fuel Oil Combustion

Residues from crude oil processing are referred to as residual fuel oils and sold under the designation of No. 5 and No. 6 or Bunker C fuel oil. Residual fuel oils contain substantial quantities of vanadium, nickel and sulfur and have a high boiling point. Home heating oils (e.g., No. 2 heating oil and diesel oils) on the other hand, have a lower boiling point than the No. 6 fuel oil, and contain much less vanadium and other metallic elements.

The vanadium concentration in crude oil shown in Table 1 represents an average value. Vanadium concentration can be as low as 1 ppm ($\approx 1\text{mg/L}$) and as high as 1400 ppm ($\approx 1.4\text{ g/L}$) depending on the source of crude oil. Generally, crude oils from the southwestern United States have the lowest level of vanadium, the Venezuelan oils the highest, and the middle Eastern oils have an average concentration of about 40 ppm ($\sim 40\text{ mg/L}$) (48). When crude oil is distilled into fractions, almost all vanadium and a significant fraction of nickel remain in the No. 6 fuel oil. The combustion of No. 6 fuel oil in electrical generating plants and commercial boilers contributes substantial quantities of nickel and vanadium to the atmosphere. In 1968, 31 billion gallons (about $115 \times 10^9\text{ L}$) of residual oil were burned in the United States. Considering that the average content of vanadium was 172 ppm ($\approx 170\text{ mg/L}$) (56% of residual fuel oil was obtained from Venezuelan crude oil) approximately 19,000 tons (17,000 metric tons) were available for discharge into the atmosphere. A report prepared for the Environmental Protection Agency (49) estimated that 90% or about 17,000 tons ($\approx 15,000\text{ metric tons}$) was emitted into the atmosphere. In 1970, the level of entry of vanadium into the atmosphere in the United States was estimated to be between 14,000 and 22,000 tons (48) [Compare this to the

estimated world production of vanadium of 18,000 tons in 1971 (21)]. The information on the average size of emitted particles containing vanadium is limited; from ambient air sampling data it is known, however, that vanadium is contained in submicron particles. Bowden et al. (50) suggested that vanadium can be emitted from combustion sources as V_2O_3 , V_2O_4 , V_2O_5 , $2\text{NiO} \cdot \text{V}_2\text{O}_5$, $\text{Fe}_2\text{O}_3 \cdot \text{V}_2\text{O}_5$, and $5\text{Na}_2\text{O} \cdot \text{V}_2\text{O}_4 \cdot 11\text{V}_2\text{O}_5$. In 1968, the emission of nickel from all stationary sources was about 6,000 tons (51). The contribution from the combustion of residual fuel oil was some 4800 tons (4370 metric tons) (51). Using the estimates given below in Table 3, the amount of nickel emitted to the atmosphere from the combustion of residual fuel oil in 1977 was about 8300 tons (7550 metric tons).

Emissions from Coal Combustion

Combustion of coal for electric power generation and space heating is the principal human activity that rapidly mobilizes large quantities of metallic elements. In 1970, the annual consumption of bituminous coal and lignite in the United States was 516 million tons (465 million metric tons; 62% for electric power, 19.5% for space heating and other uses, and 18.5% for coke production) (52). In 1977, the consumption increased to about 620 million tons (564 million metric tons) and about 77% of it was used for electrical power production (53). By 1995, the coal demand for electrical power production in the United States is expected to be 900 million tons (820 million metric tons) (54). The world consumption of coal in 1977 was 4 billion tons (3.63 billion metric tons) and about 60 percent was expended in electrical power plants (55).

The maximum possible annual release of a given metallic element can be estimated by multiplying the amount of coal burned by its concentration in coal. Table 2 gives such emission estimates for metallic elements that are most volatile. In making these estimates it has been assumed that each MWh of electrical energy requires about 400 kg of coal (17, 56), that metallic elements are present at their average concentrations, and that the total amount of each element is emitted into the atmosphere.

Metallic elements mobilized by coal combustion are partitioned between the slag or bottom ash, and fly ash; some may temporarily remain in the gaseous state. Chalcophile elements (i.e., those which readily form sulfides) tend to be associated in coal with fossilized organic matter. During combustion they are volatilized and later condensed onto the

Table 2. Estimates of metallic element mobilization by the combustion of fossil fuels.

Element	Element mobilization, 10 ³ tons			Total trace element mobilization in U.S.
	Coal combustion ^a	Fuel oil combustion ^b	Gasoline combustion ^c	
Be	15	< 0.0001	0.0003	15
Mg	1200	0.31	0.0009	1200
Al	6000	0.075	0.0033	6000
Sc	3	0.0001		3
Li	39	0.004		39
V	15	12.1	0.0001	27
Cr	6	0.192	0.056	6
Mn	30	0.06	3.1 ^d	33
Fe	6000	2.1	0.35	6002
Co	15	0.03		15
Ni	9	8.14	0.03	17
Cu	9	0.07	0.046	9
Zn	30	0.18	0.053	30
Ga	4.2	0.0015		4
As	27	0.06	0.0004	27
Se	1.8	0.01	0.02	2
Rb	60			60
Sr	300	0.06		300
Mo	3	1.48		5
Cd	0.3	0.0015	0.005	1
Sb	2.4		0.008	2
Ba	300	0.444		300
La	6	0.0007		6
Ce	10.2	0.0015		10
Pb	15	0.34	110.7 ^{e,f}	126

^aIn 1977, approximately 600 million tons of coal were consumed in the U.S. for power production and space heating.

^bIn 1977, approximately 40 billion gallons of residual fuel oil were consumed in the U.S.

^cIn 1977, approximately 110 billion gallons of gasoline were consumed in the U.S.

^dReflects a use rate of 0.125 g Mn/gal; in 1977, only 20% of gasoline consumed contained Mn at this concentration.

^eRepresents an average value for premium, regular and low-lead grades.

^fIn 1977, 80% of gasoline contained Pb fuel additives.

surface of fly ash particles. Because the surface area per unit mass increases with decreasing particles size, the concentration of metallic elements that are volatilized during combustion tends to increase in the submicron range of particles size (17, 45, 55, 57-71). Submicron particles are the most difficult to collect by the currently used pollution control devices, and the annual release estimates given in Table 2 may be surprisingly accurate for chalcophile elements, such as As, Cd, Cu, Ga, Pb, Sb, Se and Zn.

Several empirical relationships have been proposed connecting the partitioning tendency either to Goldschmidt's geochemical classification (58) or to different physical and chemical properties such as the affinity to organic matter or the boiling points of metal oxides and sulfides (55). However, these empirical relationships are only partially valid because the partitioning also depends on variables related to the particular coal burning technology used, e.g., the method of coal preparation and feeding to the combustion chamber, the

temperature in the combustion chamber, and the type of coal being burned. An example of the partitioning reported by Klein et al. (17) for a coal burning power plant is given in Table 3.

According to a model proposed by Natusch et al. (62), the surface concentrations of volatilized elements (such as As, Cd, Cu, Ga, Pb, Sb, Se and Zn) are inversely proportional to the particle diameter. Another model proposed by Flagan and Friedlander (70) predicts that the surface concentrations are inversely proportional to the square of the particle size. Both relationships hold well for particle diameters between 0.5 and 10 μ m, but fail in the submicron range, predicting that the surface concentration will continue to increase with decreasing particle diameters.

A more complex model proposed by Smith and co-workers (55, 64, 65) predicts two distinct particle size distributions for fly ash particles (bimodal distribution). Bimodal distribution in fly ash particles has been reported by McElroy et al. (54). One distribution is dominated by submicron particles in

the size range from 0.01 to 0.5 μm . It has been suggested by Smith and co-workers (55, 64, 65) that these submicron particles are produced by the bursting of larger particles caused by rapid gas release. Many of these large particles appear to be either hollow spheres (cenospheres) or hollow spheres packed with smaller spheres (plerospheres). The second particle size distribution is dominated by mineral fragments (1–40 μm) coated to some extent with condensed volatilized elements. According to Smith's model the surface concentration of condensed metallic elements reaches a maximum value in the submicron range (0.01–0.5 μm).

There is very little information on the chemical

form of metallic elements in fly ash particles. However, because coal combustion is carried out with excess air, and sulfur and chlorine are present in the feed coal, it is likely that metals will form oxides, sulfates, and chlorides beside remaining, to some extent, in elemental form. Determination of the chemical form in which an element exists is important because it will influence its bioavailability, particularly if a particle remains in the respiratory tract only for a short time. It is not clear, however, to what extent the absorption of a metal depends on the chemical form when the particles remain in the lungs for a long time. Collin (72) suggested that fly ash particles have three distinct layers. The outer-

Table 3. Partitioning of metallic elements between bottom ash and fly ash in a 290 MW cyclone-fed power plant burning bituminous coal.^a

Element	Element concentration, ppm ^b				Concentration ratios		
	Coal	Slag	Inlet fly ash	Outlet fly ash	Slag/coal	(Inlet fly ash)/slag	(Outlet fly ash)/(inlet fly ash)
Al	10,440	102,300	90,900	76,000	9.8	0.9	0.8
As	4.45	18	110	440	3.6	6.1	4.0
Ba	65	500	465	750	7.7	0.9	1.6
Br	3.7	2	4		0.5	2.0	
Ca	4,340	46,000	25,200	32,000	10.6	0.5	1.3
Cd	0.47	1.1	8.0	51	2.3	7.3	6.4
Ce	8.2	84	84	120	10.2	1.0	1.4
Cl	914	≤ 100	≤ 200		≤ 0.1	~ 1	
Co	2.9	20.8	39	65	7.2	1.9	1.7
Cr	18	152	300	900	8.4	2.0	3.0
Cs	1.1	7.7	13	27	7.0	1.7	2.1
Cu	8.3	20	140		2.4	7.0	
Eu	0.1	1.1	1.3	1.3	11.0	1.2	1.0
Fe	10,850	112,000	121,100	150,000	10.3	1.1	1.2
Ga	4.5	5	81		1.1	16.2	
Hf	0.4	4.6	4.1	5.0	11.5	0.9	1.2
Hg	0.122	0.028	0.050		0.2	1.8	
K	1,540	15,800	20,000	24,000	10.3	1.3	1.2
La	3.8	42	40	42	11.0	1.0	1.0
Mg	1,210	12,400	10,600		10.2	0.9	
Mn	33.8	295	298	430	8.7	1.0	1.4
Na	696	5,000	10,100	11,300	7.2	2.0	1.1
Ni	16	85	207		5.3	2.5	
Pb	4.9	6.2	80	650	1.3	12.9	8.1
Rb	15.5	102	155	190	6.6	1.5	1.2
Sb	0.5	0.64	12	55	1.3	18.8	4.6
Sc	2.2	20.8	26	36	9.5	1.2	1.4
Se	2.2	0.080	25	88	0.0	310	3.5
Si	23,100	229,000	196,000		9.9	0.9	
Sm	1.0	8.2	10.5	9	8.2	1.3	0.9
Sr	23	170	250		7.4	1.5	
Ta	0.11	0.95	1.4	1.8	8.6	1.5	1.3
Th	2.1	15	20	26	7.1	1.3	1.3
Ti	506	4,100	5,980	10,000	8.1	1.5	1.7
U	2.18	14.9	30.1		6.8	2.0	
V	28.5	260	440	1,180	9.1	1.7	2.7
Zn	46	100	740	5,900	2.2	7.4	8.0

^aData from Klein et al. (17); coal analysis: moisture 11.1%; volatile matter 34.7%; fixed carbon 42.8%; ash 10.4%; sulfur 3.1%; 11,390 BTU/lb.

^bAll analytical data by NAA except: Cu, Ga, Ni, and Sr by XRF; Hg by AA; Se by GCMS and Cd, Pb, and Zn by IDSSMS; values for As and for Rb are averages of NAA and XRF.

most layer is strongly acidic. This would indicate that the elements at the surface are in the form of sulfates and chlorides. In solubility studies with fly ash from an electrostatic precipitator, As, B, Cd, F, Mo and Se were readily dissolved in a 0.1N HNO₃ solution (72). Deposition in the lungs of particles smaller than 5 μ m increases rapidly (74-76). If the metallic elements are contained in an acidic layer, the uptake rate for many of them from fly ash particles would be very high. As already pointed out, in considering the exposure to metallic elements from fly ash particles, the presence of organic compounds such as polynuclear aromatics and heterocyclic compounds has to be taken into account, as well as the structure and composition of the matrix which contains several crystalline phases, and an aluminosilicate amorphous glassy material (3, 77).

Some actual data on the enrichment of metallic elements on particles of different size of fly ash (78) are shown in Table 4. Although the data do not extend to submicron particle size, they clearly demonstrate that the concentration of elements such as V, Cr, Mn, Co, Ni, Cu, Zn, Ga, As, Se, Sr, Mo, Cd, Sb, Ba and Pb increases with decreasing particle size of fly ash.

Exposure to submicron particles from coal combustion is usually confined to the areas adjacent to

power plants and commercial boilers, but if meteorological conditions are appropriate particles can remain aloft for an extended time and be transported great distances from their origin.

The collection efficiency of particulate air pollution control devices (Venturi scrubbers, electrostatic precipitators and bag filters) can drop rapidly for particles smaller than 0.5 μ m and can be reduced to as little as 10% (79), depending on the device chosen for control of particulate matter. It is conceivable that a substantial amount of metallic elements can therefore escape air pollution control devices. In comparing these devices, care must be taken to determine how collection efficiencies are measured. Most of the collection efficiencies are determined on a mass basis and therefore do not accurately measure the ability of the device to prevent the release of submicron fly ash particles. In this regard, submicron fly ash particles contribute only 0.5 to 1.3% to the total mass of fly ash produced during combustion (54). In Figure 1, collection efficiencies plotted as a function of particle diameter clearly indicate the effectiveness of different devices on removing submicron particles. Paulson and Ramsden (81) related the poor collection efficiency of electrostatic precipitators, the most commonly used device, to the content of the microlithotype fusite in some coals. The higher the

Table 4. Concentrations of elements as a function of fly ash particle diameter.^a

Element	Concentration, mg/kg			
	18.5 μ m	6.0 μ m	3.7 μ m	2.4 μ m
Be	6.3	8.5	9.5	10.3
Mg	4700	5600	6000	6300
Al	138000	144000	133000	139000
Sc	12.6	15.3	15.8	16.0
Ti	6200	7400	7300	7700
V	86	178	244	327
Cr	28	53	64	68
Mn	208	231	269	309
Fe	25000	30900	30400	32000
Co	8.9	17.7	20.3	21.8
Ni	25	37	43	40
Cu	56	89	107	137
Zn	68	189	301	590
Ga	43	116	140	178
As	13.7	56	87	132
Se	19	59	78	198
Rb	51	56	57	57
Sr	410	540	590	700
Mo	9	28	40	50
Cd	0.4	1.6	2.8	4.6
Sb	2.6	8.3	13.0	20.6
Ba	1680	2450	3100	4100
La	62	68	67	69
Ce	113	122	123	120
Pb	73	169	226	278

^aData are from Ondov et al. (78) for a power plant fed with low-sulfur (0.46%), high-ash (23%) coal.

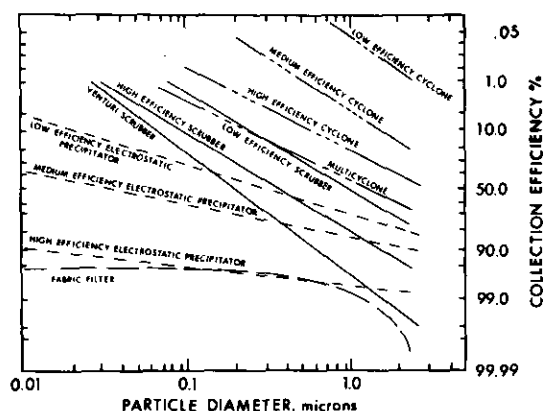


FIGURE 1. Particulate matter collection efficiencies for different types of air pollution control equipment as a function of particle diameter. Data from Vandegrift et al. (80).

content of fusite, the greater is the quantity of submicron fly ash that is produced, and the lower is the collection efficiency of the precipitator. In addition, the methods of coal preparation and feeding and the type of combustion chamber have a significant influence on the amount of fly ash that is produced and must be removed by the air pollution control equipment. Stoker-fired units emit the smallest proportion of fly ash; cyclone-fired furnaces produce high proportions of bottom ash, and pulverized coal units, which are the most common, produce the highest amount of fly ash (60–58% of the total ash) (82).

Because the metallic elements that are most readily volatilized occur in coal as sulfides, the levels of these elements can be reduced before combustion by chemical cleaning of coals. Another means to control more effectively metallic element emissions during coal combustion is the use of flue gas desulfurization equipment which is required in the United States for coal burning electrical power plants. The lime scrubber which is the most commonly used design appears to be effective in removing metallic elements that have escaped collection by other air pollution control equipment (54). These scrubbers, however, produce large amounts of sludge that substantially increase operating costs of electric utilities and will tax the capacity of land disposal sites to contain this material in an environmentally acceptable fashion. The data on removal of submicron fly ash particles by flue gas desulfurization equipment are limited (67) and make it difficult to draw general conclusions about the effectiveness of these devices for removing volatilized trace elements on submicron fly ash particles.

Flue-gas desulfurization of stack gases has been necessary to allow the use of high-sulfur coals in the United States. The development of fluidized bed combustion of coal appears to make the need for this type of external control device unnecessary (83). Reduction of sulfur oxide emissions is achieved by adding limestone or dolomite continuously along with pulverized coal to the fluidized bed combustor. Sulfur is retained as sulfate in the bed. Operating temperatures are usually much lower (500–600°C) so that volatilization of elements should be reduced. An added advantage of lower operating temperatures is a reduction in nitrogen oxide emissions. No data on emissions of submicron particles and metallic compounds, however, could be found.

Concentration Ranges of Metallic Elements in Urban Ambient Air

Although the human exposure to metallic elements in urban air pollution has to be determined on a case by case basis because it depends largely on local conditions, it may nevertheless be useful to indicate the order of magnitude of air borne metallic element concentrations. Table 5, taken from Thompson (22), gives overall concentrations of metallic and nonmetallic elements contained in atmospheric particulates. These data are based on the analysis of "hi-volume" samples collected by continuous air sampling for a 10-day period in Cincinnati, Denver, St. Louis, Washington, Chicago and Philadelphia during December 1969 through April 1970. Table 5 shows that the concentration of metals can be expected to vary within a wide range from about 1 to 10^5 . In interpreting these results, one should not forget that fossil fuel combustion is not the only source of these elements in urban air, and that natural and industrial sources also make a significant contribution. One should also keep in mind that the metallic elements in atmospheric particulates are contained in a variety of inorganic and possibly organic compounds embedded in solid mineral and carbonaceous matrices of different structure and that this complex physicochemical composition determines to a large extent the biological effects of atmospheric particles.

Exposure to metals and metal compounds contained in suspended particulates occurs simultaneously with exposure to a variety of airborne organic compounds which are either natural or man-made products, and are present in the form of either volatile substances or nonvolatile compounds condensed on particles (84) many of which are potentially carcinogenic (71) or mutagenic, or may interact with metallic contaminants (85) by enhanc-

Table 5. Range and typical values ($\mu\text{g}/\text{m}^3$) for elements in particulates collected from ambient air.^{a,b}

Element	Elements in particulates, $\mu\text{g}/\text{m}^3$		
	Low	High	Typical
H Total	3,000	11,600	5,000
"Inorganic" ^c	1,600	4,700	3,000
He		Not sought	
Li	2	20	4
Be	0.01	0.6	0.2
B	3	30	5
C Total	28,000	110,000	50,000
"Inorganic" ^c	15,000	50,100	25,000
N Total	2,400	9,700	4,000
"Inorganic" ^c	2,100	7,800	3,000
O		Not determined	
F	20	900	50
Ne		Not sought	
Na	500	12,000	2,000
Mg	1,000	5,000	2,000
Al	1,000	10,000	3,000
Si	4,000	45,000	10,000
P	50	600	100
S Total	3,000	11,000	5,000
"Inorganic" ^c	1,700	8,700	4,000
Cl	4	13,000	1,000
Ar		Not sought	
K	600	10,000	1,000
Ca	2,000	20,000	6,000
Se	1	10	1
Ti	150	600	200
V	1	300	30
Cr	3	50	20
Mn	30	200	100
Fe	1,500	9,000	4,000
Co	3	10	5
Ni	2	100	20
Cu	100	3,000	500
Zn	200	3,000	500
Ga	3	8	5
Ge	0.4	10	2
As	2	100	10
Se	2	20	4
Br	10	200	100
Kr		Not sought	
Rb	10	100	20
Sr	20	200	40
Y	1	5	2
Zr	2	20	4
Nb	0.3	4	0.5
Mo	0.5	10	1
Te		Not sought	
Ru	0.01	0.1	0.03
Rh	0.01	0.1	0.03
Pd	0.2	1	0.3
Ag	0.5	20	1
Cd	0.3	20	1
In	0.5	2	1
Sn	6	200	50
Sb	2	60	5
Te	0.1	0.2	0.1
I	0.01	0.1	0.4
Xe		Not sought	
Cs	0.3	3	1
Ba	10	500	100
La	2	20	5
Ce	3	20	5

Table 5. (continued)

Element	Elements in particulates, $\mu\text{g}/\text{m}^3$		
	Low	High	Typical
Pr	1	5	2
Nd	1	10	5
Sm	0.4	2	1
Eu	0.1	0.5	0.2
Gd	0.3	1	0.6
Tb	0.05	0.2	0.1
Dy	0.2	1	0.2
Ho	0.03	0.1	0.3
Er	0.3	0.5	0.3
Tm	0.03	0.1	0.06
Yb	0.05	0.3	0.1
Lu	0.02	0.3	0.05
Hf	0.04	0.2	0.05
Ta	0.1	0.3	0.2
W	0.1	2	1
Re	0.01	0.06	0.02
Os	0.02	0.06	0.04
Ir	0.01	0.06	0.02
Pt	0.02	0.06	0.04
Au	0.02	0.1	0.06
Hg	0.02	0.1	0.04
Tl	0.01	0.1	0.02
Pb	300	5,000	2,000
Bi	0.02	2	0.6
Po		Not sought	
At		Not sought	
Rn		Not sought	
Fr		Not sought	
Ra		Not sought	
Ac		Not sought	
Th	0.05	1	0.2
Pa		Not sought	
U	0.05	2	0.2
Transuranic elements	Not sought		

*Data of Thompson et al. (22).

^bChicago, Cincinnati, Denver, Philadelphia, St. Louis, Washington, DC.

ing or inhibiting their action. Several hundred aliphatic hydrocarbons have been identified as urban air pollutants by the California Air Resources Board (86, 87). Along with alkanes, alkenes such as ethylene (88), alkynes such as acetylene (89), cycloalkanes and alkenes (90) have been reported as urban air pollutants. Benzene, a human carcinogen, toluene, and many other aromatic hydrocarbons have been detected in some industrialized urban areas (91). However, particular attention has been paid to the presence in air of polycyclic aromatic hydrocarbons because compounds such as benzo-(a)pyrene, contained in atmospheric particulates, are probably human carcinogens. Atmospheric levels of these compounds have been recently reviewed by Santodonato, Howard and Basu (92). This report provides information on measured concentrations in different types of atmospheric environments for 65 individual polycyclic organic compounds or groups

of compounds. The long list of organic air pollutants also includes more than 50 halogenated hydrocarbons. The highly toxic polychlorinated dibenzo-*p*-dioxins (93), dibenzofurans (94), biphenyls (95), and phenols (96) have been identified in ambient air samples. Aliphatic and aromatic aldehydes are found in air as a result of incomplete combustion in automotive engines and incinerators, and as products of photochemical reactions in which alkenes are present (97). Fifteen dicarboxylic acids have been found in atmospheric particulates during a smog episode (98). Human carcinogens bis-(chloromethyl) ether and vinyl chloride have also been identified as air pollutants (99). Among the organic nitrogen compounds measured in polluted air are *N*-nitroso compounds such as dimethylnitrosamine (100). Several azaheterocyclic compounds have been found in the benzene soluble fraction of urban suspended particulate matter sampled in five U.S.

cities (16), and some 110 heteroatomic organic compounds containing sulfur, nitrogen and oxygen were identified in the vapor phase of ambient air.

The concentrations of different organic compounds in air are highly variable and range from below the threshold of detection to levels of the order of parts per million. Since the sampling methods are often designed to collect specific compounds, only a small number of organic compounds present in air are usually identified.

Evaluation of Carcinogenicity: Animal Bioassays

The question discussed in this section is to what extent can animal bioassays help answer questions regarding carcinogenicity of metals and metal compounds contained in fossil fuel combustion products.

Among some 80 elements which exhibit metallic or metallike properties, bioassays with experimental animals provided some evidence—by no means always adequate or sufficient—for the carcinogenicity of about 20 individual metals or metallike elements either in elemental state or in the form of inorganic or metallo-organic compounds, or complexes involving organic ligands (101-108). Some of these elements are carcinogenic because they are naturally radioactive, e.g., U and Th (109). They will not be further discussed, although a complete appraisal of carcinogenicity of fossil fuel combustion products has to take this into consideration. All these elements have been detected in measurable quantities in particulate air pollutants collected in ambient air.

This list of potential metal carcinogens in ambient air can be considerably reduced if we eliminate the elements which have been reported as carcinogenic only in chemical or physical forms not likely to occur in fossil fuel combustion products or secondary air pollutants (110-113), and/or elements which produced only localized tumors at the site of injection (114-116). Application of these criteria immediately eliminates from further consideration Al, Ag, Cu, Fe, Gd, Hg, Pt, Ti, Yb, and Zn.

In addition, manganese, tin, lead and cobalt should be also removed from the list. Manganese acetylacetonate suspended in trioctanoin was reported to produce local sarcomas in rats after intramuscular injection (110). This would put manganese in the class of elements and compounds listed above. However, in another experiment, an increased incidence of lymphosarcoma was observed in a group of DBA/1 mice treated with manganese chloride (117). Sodium chlorostannate administered

in food induced in one experiment several different tumors in rats but the increase in incidence was not statistically significant (118). For lead, there is sufficient evidence of carcinogenicity in experimental animals only if it is administered in the form of lead acetate, lead subacetate and lead phosphate, compounds not likely to be found in fossil fuel combustion products and related air pollutants. The evidence for the carcinogenicity of cobalt is also limited to injection site fibrosarcomas or rhabdomyosarcomas and to possible distant site sarcomas following injection of cobalt chloride solutions (119).

As judged by the evidence provided by animal bioassays for carcinogenicity, this leaves six metallic or metallike elements and their compounds—Be, Cd, Cr, Ni, Sb and Se—as potential human chemical carcinogens contained in air pollutants derived from fossil fuel combustion. Some of this evidence has been evaluated by an *ad hoc* Working Group of the International Agency for Research on Cancer (102). The available bioassay data for elemental beryllium, beryllium oxide, beryllium phosphate, beryllium sulfate, for elemental cadmium, cadmium chloride, cadmium oxide, cadmium sulfate, and cadmium sulfide, for calcium chromate and some insoluble chromium (VI) compounds, and for elemental nickel and nickel subsulfide have been found to provide sufficient evidence of carcinogenicity in experimental animals. Using the same criteria, there seems to be sufficient evidence that selenium sulfide (120) and, probably, antimony (III) oxide (121, 122) are carcinogenic in experimental animals.

Only in some cases such as arsenic (123) and perhaps iron (124) have the negative results of bioassays been evaluated with the same attention that is paid to the positive results. It is also fairly rare that the negative results are even reported although there are cases e.g. germanium, tellurium, tin, and vanadium (125-128). We can assume, however, that at present there is no evidence of carcinogenicity for other metallic elements and their compounds.

The definitive criterion for evaluating the predictive value of whole animal bioassays is the consistency of bioassay results with the results of epidemiological studies and human case reports. According to an *ad hoc* working group of the International Agency for Research on Cancer (IARC) (102), sufficient evidence in human subjects exist for the carcinogenicity of inorganic arsenic compounds (both for general population and occupational exposure) and for chromium and certain inorganic chromium compounds (occupational exposure), although the relative contributions to carcinogenic risk of metallic chromium, chromium (III) and chromium (VI) compounds or soluble versus

insoluble chromium compounds cannot be evaluated (129); sufficient evidence is also available for the process of nickel refining and for underground hematite mining. Since such evidence does not exist for surface mining of hematite, it is likely that other factors such as radioactivity or silica are involved. The evidence for the carcinogenicity in human subjects of nickel, beryllium and cadmium, and some of their compounds is limited; it is inadequate for lead and certain organic lead compounds, and for hematite.

The conclusions of a workshop on the role of metals in carcinogenesis held in Atlanta in 1980 (106, 129) are somewhat different: there is good evidence from human case reports and/or epidemiological studies that specific compounds of arsenic, chromium, nickel, beryllium and cadmium contribute to human cancer.

Sufficient evidence also exists for carcinogenicity in human subjects of compounds containing naturally radioactive elements such as thorium and uranium (130).

Based on the evaluations provided by IARC (102, 123), the predictive value of long-term animal bioassays seems to be good for chromium and some inorganic chromium compounds, and probably for hematite, nickel and certain nickel compounds. It is limited for beryllium, cadmium and some of their inorganic compounds and inadequate for inorganic arsenic compounds and some soluble inorganic compounds of lead. In view of the Atlanta meeting (106, 129), there seems to be adequate correlation between whole animal bioassay results and human evidence for the carcinogenicity of some specific chemical forms of chromium, nickel, and beryllium, and inadequate correlation for cadmium, lead and arsenic.

Exposure to metallic elements and metal compounds contained in submicron particles from fossil fuel combustion occurs jointly with a variety of other inorganic compounds and many organic substances as mentioned in the previous section. One could argue that mixed exposure to more than one metal and to compounds containing the metal under consideration in different oxidation states, also occurs in occupational exposure. This is true, but the levels of occupational exposure to metals are usually much higher, and metals are the dominant exposure. When they are not, as in underground hematite mining, the results of epidemiological studies are inconclusive. The exposure to a given metal contained in particulate air pollution is much lower, this component of exposure is usually not the dominant one, and various confounding factors are always present, including different mineral and

carbonaceous matrices, other metallic elements, possibly natural radioactive elements, and a rather large number of organic compounds.

Specification of inorganic and organic compounds contained in particulate air pollution is usually not available, and, in addition, its composition may change from case to case much more drastically than in occupational exposure. This may influence the bioavailability of the metal under consideration, and consequently the dose. However, a more precise knowledge of chemical composition of airborne particles may not help very much because of possible interactions. In addition, usually no information is available on the previous exposure to airborne pollutants, and on exposure to metallic elements contained in food which is in most cases the major source of trace elements.

Our present knowledge on metal-metal interactions is very limited; this limitation is even more serious with regard to interactions between metal compounds and organic molecules possibly carcinogenic *per se*. Nordberg and Andersen have recently reviewed metal interactions in carcinogenesis (85). Fe_2O_3 (131), MgO (132), TiO_2 (133) and possibly other mineral dusts appear strongly to potentiate carcinogenic activity of organic compounds such as benzo(a)pyrene and diethylnitrosamine (134). Concurrent metal exposures seem to change the localization of tumors caused by nitrosamines significantly and reduce the latency time (135). The oxidation state of a metal carcinogen may be changed by another metal or other compounds present in the mixture (85). Nickel carcinogenesis has been reported as antagonized by manganese (136), and potentiated by some organic compounds such as benzo(a)pyrene (137).

All this seems to indicate that the predictive value of whole animal bioassays for metal carcinogenesis, if carried out with pure compounds possibly at maximum tolerated doses, would be rather low with regard to metallic elements in fossil fuel combustion products. Whole animal bioassays are certainly not a method of choice. One possible option would be to conduct such bioassays using samples of airborne particulate matter. This, however, is not a practical proposition, because of cost and the limited value that such bioassays would have, one reason being that the composition of suspended particulate matter derived from fossil fuel combustion depends considerably on the fuel, combustion technology and operational conditions used. For these reasons, short-term bioassays seems to be a much more attractive approach for carcinogenicity screening of metal compounds contained in complex mixtures.

Evaluation of Mutagenicity and Carcinogenicity: Short-Term Bioassays

Methodological details of short-term bioassays for mutagenicity and carcinogenicity, including tests with bacteria, yeasts and molds, mammalian cells and whole animals have been described in several reviews (133-142). Several reports are available which compile and/or evaluate the results of short-term testing of groups, of metals and metal compounds using various methods (101, 105, 119, 143-149), the application of specific short-term tests or groups of such tests to different metals and metal compounds (150-164), or specific metals such as arsenic (123, 165) beryllium (123, 166) cadmium (167, 168), chromium (123, 169, 170), lead (123, 171)

and nickel (167, 172-174). Some of these results, particularly for inorganic metal compounds that are likely to occur in fossil fuel combustion products, are summarized in Tables 6-10, together with selected references. Although the tests were performed with specific metal compounds, Tables 6-10 list only the metal and its oxidation number, assuming that the oxidation state of the metallic element in the compound primarily determines the outcome of the test. This, of course, may not always be true, and in some inorganic metal compounds the active components are probably the anions such as NO_2^- rather than the cations (e.g., Na^+ or K^+). However, it seems likely that, for most metal compounds included in Tables 6 to 10, the oxidation state of the metal is the most significant property of the compound tested. Metabolic activation has, in most cases, a minor effect on the outcome of

Table 6. Some tests based on DNA damage and repair.

		Results obtained with some metal compounds ^a					
Effect/target organism/target cell	Endpoint	Positive	Negative		Inconclusive ^b	Selected references	
Growth inhibition of repair deficient bacteria							
<i>B. subtilis</i> M 45 rec ⁻ H 17 rec ⁺ ('rec-assay')	Growth inhibition of rec ⁻ strain	As ^{III}	Ag ^I	K ^I	Ru ^{III}	Be ^{II}	Kada et al. (163)
		As ^V	Al ^{III}	La ^{III}	Se ^{VI}	Cd ^{II}	
		Cr ^{VI}	Au ^{III}	Li ^I	Sn ^{II}	Co ^{II}	Kanematsu and Kada (154) Kanematsu et al. (175)
		Cs ^I	Ba ^{II}	Mg ^{II}	Sn ^{IV}	Co ^{III}	
		Ir ^{IV}	Bi ^{III}	Mn ^{VII}	Sr ^{II}	Cr ^{III}	Nakamuro et al. (176) Nishioka (152)
		Mo ^{VI}	Ca ^{II}	Mo ^{IV}	Ta ^V	Hg ^I	
		Os ^{VIII}	Ce ^{III}	Mo ^V	Tb ^{III}	Hg ^{II}	
		Pt ^{IV}	Cu ^I	Nb ^V	Th ^{IV}	Mn ^{II}	
		Rb ^{III}	Cu ^{II}	Ni ^{II}	Ti ^{III}	Sb ^{III}	
		Tl ^I	Eu ^{III}	Ni ^{III}	Ti ^{IV}	Sb ^V	
		V ^{IV}	Fe ^{II}	Pb ^{II}	Y ^{III}	Se ^{IV}	
		V ^V	Fe ^{III}	Pb ^{IV}	Zn ^{II}	Te ^{IV}	
				Ga ^{III}	Pd ^{II}	Zr ^{IV}	Te ^{VI}
				In ^{III}	Rb ^I		
<i>E. coli</i> pol A ⁻ , pol A ⁺ (‘pol A’ test)	Growth inhibition of pol A ⁻ strain		Be ^{II}				Nestmann et al. (177)
			Pb ^{II}				Rosenkranz and Poirier (178)
			Cr ^{VI}				
Unscheduled DNA synthesis <i>in vitro</i>							
Human fibroblasts	Incorporation of ³ H-TdR	Se ^{IV} Se ^{VI}					Lo et al. (179)
Reduced fidelity of DNA synthesis							
Purified DNA polymerases, synthetic or natural templates, correct substrate, incorrect substrate Mg ²⁺	Rates of incorporation of [α - ³² P] complementary and [³ H] non-complementary nucleotides; frequency of incorporation of noncomplementary nucleotides; reversion frequency of phage copying mutant $\phi \times 174$ <i>in vitro</i>	Ag ^I		Al ^{III}		Co ^{II}	Loeb et al. (180, 181) Loeb and Zakour (182)
		Be ^{II}		As ^V		Cr ^{VI}	
		Cd ^{II}		Ba ^{II}		Cu ^{II}	Miyaki et al. (183) Seal et al. (184)
		Cr ^{II}		Ca ^{II}		Fe ^{IV}	
		Cr ^{III}		Fe ^{II}		Hg ^{II}	Sirover and Loeb (155, 156)
		Cr ^{VI}		K ^I		Zn ^{III}	
		Mn ^{II}		Mg ^{II}			Tkeshelashvili et al. (157, 158)
		Ni ^{II}		Na ^I			
		Pb ^{II}		Rb ^I			Zakour et al. (151)
				Se ^{IV}			
			Sr ^{II}				

^aAlthough the test were carried out with specific compounds, only the oxidation state of the metal is indicated.

^bReported positive by some authors, negative or uncertain by others.

bacterial tests; however, it may influence the biological activity of metals which may form compounds in several oxidation states (e.g., Cr in Table 7).

Although the data presented are not complete, they nevertheless illustrate several points that may be useful to remember. Positive results in short-term tests have been more frequently obtained with some metals which tend preferentially to accumulate in submicron particles of the fly ash (e.g., As, Be, Cd, Cr, Cu, Mo, Ni, Pb, Sb, Se and V) than with metals which are more likely to be

found in the bottom ash (e.g., Al, Ba, Co, Fe, Sr and Ti). The results for elements such as Be, Cd, Cr, Ni, Pb and Sb generally agree with the results of animal bioassays. The results for arsenic do not always correlate with findings of epidemiological studies on the carcinogenicity of this element. It is evident that several short-term bioassays should be used in order to detect different types of effects of metals. On the whole, the amount of data available, and their distribution among different short-term tests does not permit any definitive conclusions with regard to suitability of tests for metal com-

Table 7. Some gene mutation tests in bacteria and "induct" test.

Results with some metal compounds ^a					
Test and strains used	Endpoint	Positive	Negative	Incon- clusive ^b	Selected references
Reverse mutations of auxotrophs					
<i>Salmonella</i> /Ames test (TA tester strains, his ⁻)	his ⁺ colonies	Cd ^{II} Cr ^{VI} Se ^{VI} Pt ^{II} Zn ^{II}	Cr ^{III} Se ^{IV} Pb ^{II} As ^{III} As ^V Be ^{II}	Fe ^{II}	Brusick et al. (185) Kalinina et al. (186) Löfroth and Ames, (187) Nestmann et al. (177) Petrilli and DeFlora (188) Petrilli and DeFlora (189, 190) Simmon (191) Tamaro et al. (192) Tamaro et al. (193) Tindall et al. (194)
<i>Salmonella</i> /Ames test with metabolic activation (TA tester strains)	his ⁺ colonies	Fe ^{II} Zn ^{II}	Be ^{II} Cr ^{III} Cr ^{VI} Pb ^{II}	Cd ^{II}	Brusick et al. (185) Nestmann et al. (177) Petrilli and DeFlora (188) Petrilli and DeFlora, (189, 190) Poluhina et al. (195) Simmon (191) Kalinina et al. (186)
<i>Salmonella</i> , host- mediated assay (mouse) (TA tester strains)	his ⁺ colonies	Cd ^{II} Zn ^{II}			
<i>E. coli</i> auxotrophic strains such as B/WP2	Prototrophic colonies	Cr ^{VI} Pb ^{IV} Rh ^{III} V ^{IV}	As ^{III}		Hemmerly and Demerec (196) Ishizawa (197) Kanematsu and Kada (154) Nestmann et al. (177) Nishioka (152) Tamaro et al. (192) Tamaro et al. (193) Tindall et al. (194) Venitt and Levy (198) Green et al. (199) Nestmann et al. (177)
Fluctuation test, <i>E. coli</i> auxotrophs	Growth of mutants	Cr ^{VI}	Ni ^{II}		Tindall et al. (194) Brusick et al. (185) Speck et al. (200) Tamaro et al. (192) Tamaro et al. (193)
"Induct" test Prophage λ induction, <i>E. coli</i> K-12 (λ)	Infective centers on nonlysogens	Pt ^{IIc}	Be ^{IIc} Pb ^{II}		

^aAlthough the test were carried out with specific compounds, only the oxidation state of the metal is indicated.

^bReported positive by some authors, negative or uncertain by others.

^ccis-Pt(NH₃)₂ Cl₂.

Table 8. *In vitro* morphological transformation of mammalian cells.

Effect and target cells	Endpoint	Results obtained with some metal compounds ^a			Selected references
		Positive	Negative	Inconclusive ^b	
<i>In vitro</i> transformation; Syrian hamster embryo cells	Transformed colonies	As ^V Be ^{II} Cd ^{II} Cr ^{VI} Ni ^{II} Pb ^{II}	Al ^{III} Fe ^{III} Ni ^{II} Ti ^{IV} W ^{VI} Zn ^{II}		DiPaolo and Casto, (159) DiPaolo et al. (201) Pienta et al. (202)
Enhancement of viral transformation; Syrian hamster embryo cells	SA7 foci ^c	Ag ^I Hg ^{II} As ^{III} Mn ^{II} Be ^{II} Ni ^{II} Cd ^{II} Pb ^{II} Co ^{II} Pt ^{IV} Cr ^{VI} Sb ^{III} Cu ^I Ti ^I Cu ^{II} W ^{VI} Fe ^{II}	Al ^{III} Ba ^{II} Ca ^{II} Li ^I Mg ^{II} Na ^I Sr ^{II} Ti ^{IV}	Zn ^{II}	Casto et al. (160) DiPaolo et al. (201)
Promotion of transformation by BaP, synergism of BaP and metal compounds; Syrian hamster embryo cells	Transformed colonies	Cd ^{II} Cr ^{VI} Ni ^{II}	Cr ^{III} Zn ^{II}		Rivedal and Sanner (203)

^aAlthough the test were carried out with specific compounds, only the oxidation state of the metal is indicated.

^bReported positive by some authors, negative or uncertain by others.

^cSimian adenovirus SA7.

Table 9. Some tests with yeasts.

Target organisms, strains	Endpoint	Results with some metal compounds ^a			Selected references
		Positive	Negative	Inconclusive ^b	
<i>S. cerevisiae</i> , D ₃ , D ₄ , D ₅ , SBTD, S/MB-13D etc.	Mutation	Mn ^{II}	Ca ^{II} Fe ^{II} Cd ^{II} Ge ^{II} Co ^{II} Mg ^{II} Cr ^{II} Ni ^{II} Cu ^{II} Ti ^{II}		Baranowska et al. (204) Nestmann et al. (177) Putrament et al. (205) Simmon (206)
	Miotic recombination	Cr ^{VI}	Be ^{II} Mn ^{II} Pb ^{II}		
<i>Schizosaccharomyces pombe</i> , 972h ⁻ ; ade 7, 50/150; etc.	Mutation Gene conversion	Cr ^{VI}		Cr ^{VI}	Bonatti et al. (207)

^aAlthough the test were carried out with specific compounds, only the oxidation state of the metal is indicated.

^bReported positive by some authors, negative or uncertain by others.

pounds, and how good their predictiveness for carcinogenicity in experimental animals may be. Nonetheless, it appears that tests based on fidelity of DNA synthesis, DNA-repair deficiency, and transformation of mammalian cells are more suitable for metal compounds than tests based on bacterial gene mutations.

In spite of limited information available, short-term tests have several advantages compared to whole animal bioassays as screening procedures for

the large number of metal compounds which still require evaluation. They are less costly and less time-consuming, and testing of mixtures and identifying interactions (203, 235) may be easier with such tests than in whole animal bioassays. Also they are more sensitive so that tests can be carried out at metal concentrations which are much more comparable to human exposure levels than are the doses used in whole animal bioassays. For example, the reversion of *S. typhimurium* his⁻ was measured

at chromium levels of a few nanomoles (less than 1 μg) (152). Also, fairly good dose response can be obtained in some tests (184). Another advantage is that the activity of metal compounds known to be present in fossil fuel combustion products or urban air pollutants could be tested in human cells by

using such endpoints as sister-chromatid exchange or stimulation of DNA repair (237).

Since many short-term tests are based on mutagenesis in test systems, they should be predictive, at least in principle, of the potential of a chemical for inducing heritable genetic disease (238). How-

Table 10. Some cytogenetic tests.

		Results with some metal compounds ^a			
Organism, test system	Endpoint	Positive	Negative	Inconclusive ^b	Selected references
<i>In vitro</i>					
Human leukocytes lymphocyte, or fibroblast cultures	Chromosome aberrations	As ^{III}	Be ^{II}	Cd ^{II}	Beek and Obe (208, 209)
		As ^V	Co ^{II}	Cr ^{II}	Deknuds and Deminatti (164)
		Cr ^{VI}	Fe ^{II}	Pb ^{II}	MacRae et al. (210)
		Sb ^{III}	Hg ^{II}	Se ^{IV}	Nakamuro et al. (176, 211)
		Te ^{IV}	Ni ^{II}	Se ^{VI}	Newmann et al. (212)
	Zn ^{II}	V ^V		Oppenheim and Fishbein (213)	
				Paton and Allison (161)	Petres and Hundelker (214)
	Sister chromatid exchanges	Cr ^{VI}		Cr ^{III}	Stella et al. (215)
		Ni ^{II}		Pb ^{II}	Wulf (216)
Chinese hamster cell cultures (CAL, CHO, Don, Hy, V79/A)	Chromosome aberrations	Cd ^{II}	Cr ^{II}	Cr ^{III}	Bauchinger and Schmid (217)
		Cr ^{VI}	Pb ^{II}		Levis and Majone (218)
					MacRae et al. (210)
					Majone and Levis (219)
					Newbold et al. (220)
	Sister chromatid exchanges	As ^{IV}	Cd ^{II}	Cr ^{III}	Ohno et al. (221)
		As ^V	Fe ^{II}		Röhr and Bauchinger (222)
		Cr ^{VI}	Fe ^{III}		Tsuda and Kato (223)
		Ni ^{II}	Se ^{IV}		
			Sn ^{II}		
			Ti ^{III}		
			Zr ^{III}		
C3H mouse mammary carcinoma FM3A cell cultures	Chromosome aberrations	Cr ^{VI}	Cd ^{II}		Umeda and Nashimura (162)
		Mn ^{VII}	Cr ^{III}		
		Ni ^{II}	Hg ^{II}		
<i>In vivo</i>					
Human subjects, occupational and other exposure (peripheral lymphocytes)	Chromosome aberrations	As ^c	Pb ^c	As ^d	Bigaliev et al. (224)
		Pb ^c	Cd ^c	Ni ^c	Bijlsma and deFrance (225)
		Cr ^c			Deknuds et al. (226)
		Cr ^{Vlc}			Forni et al. (227)
		Hg ^c			Högstedt et al. (228)
	Zn ^c			Nordenson et al. (229)	
				Nordenson et al. (230)	O'Riordan and Evans (231)
				O'Riordan et al. (232)	Petres et al. (233)
	Sister chromatid exchanges			Cd ^c	Stella et al. (215)
Rat, mouse, and Chinese hamster, peritoneal cells	Chromosome aberrations	Al ^{III}			Nashed (234)
		Mg ^{II}			
Mouse, bone marrow cells	Micronuclei	Cr ^{VI}	Pb ^{II}		Watanabe et al. (235)
			Cd ^{II}		Wild, (236)

^aAlthough the test were carried out with specific compounds, only the oxidation state of the metal is indicated.

^bReported positive by some authors, negative or uncertain by others.

^cOccupational exposure, chemical form cannot be always specified.

^dTherapeutic exposure.

ever, at the present stage of development, the usefulness of short-term tests is very limited for carcinogenic risk estimation and even more so for estimating the risk of heritable genetic disease (239).

Most testing of metallic elements was performed with single compounds, not necessarily those expected to occur in fossil fuel combustion products. The available results, therefore, do not bring us much nearer to answering the question about their usefulness in estimating the contribution of trace metals to the mutagenic or carcinogenic potential of fossil fuel combustion products where metal compounds occur in complex mixtures of inorganic and organic compounds embedded in mineral or carbonaceous matrices.

In combination with appropriate extractions and/or chemical separations, short-term tests have been used for detecting mutagenic and potential carcinogenic activity of particulate air pollutants (240,241). This approach is discussed in several other papers presented at this meeting, and we will limit ourselves only to a few remarks concerning the usefulness of such procedures for evaluating the activity of metal compounds in airborne particles, although only a few such studies have been devoted to the study of inorganic components contained in suspended particulate matter. Hedenstedt et al. (242) and Maxild et al. (243) investigated the mutagenicity of welding fumes. Fume particles formed during the welding of stainless steel contained Cr, Ni and small amounts of Pb, Mn, Mo and Fe. These particles were shown to be mutagenic in an assay using TA 100 and TA 98 strains of *S. typhimurium*, but fumes formed during welding of mild steel and containing mainly iron, showed no activity.

Several methodological problems have been encountered in such studies. One concerns the sampling of airborne particles. Total particulate matter is usually collected on glass filters (244). A disadvantage of total particulate matter collection is that particle size distributions are disregarded. Unsized samples may give negative or inconclusive results because submicron particles represent, on a mass basis, a small fraction of total particulates. Another disadvantage of such sampling is that chemical reactions may take place in the sample, converting the organic compounds originally adsorbed on, or absorbed in particles to new compounds which may be more or less mutagenic (245).

The temperature at which particulate samples are collected may have a significant influence on the results of short-term tests. Size-classified fly ash particles collected at 95°C from the stack of a coal burning power plant were found to be mutagenic for frameshift mutants in the Ames test, but no

mutagenicity could be detected when a hopper fly ash sample was collected with an electrostatic precipitator at 107°C (246-248). This seems to indicate that the mutagenic components of fly ash particles are adsorbed or absorbed by solid particles from the gas phase, and that there is a critical temperature above which the absorption or adsorption is not effective. Trace metal compounds largely contained in or on submicron fly ash particles are not likely to be influenced by temperatures around 100-150°C. Thus it seems that metal compounds are probably not directly responsible for mutagenicity of fly ash particles, at least not for the major part of it. A possibility still remains, however, that trace metal compounds have a significant role in modifying the mutagenic activity of organic compounds (203). Also, it has been reported that heating resulted in decomposition rather than volatilization of fly ash mutagens; the decomposition may have been catalyzed by trace elements adsorbed on the surface (246).

Solvent extraction may also cause loss or modification of mutagenic potency, and possible synergistic or antagonistic interactions may disappear if interacting components are extracted in different solvent fractions. A mixture of five fractions of benzene extract of urban air pollutant particles contained 30% more mutagenic activity than the sum of fractions, indicating that such synergism does exist (249).

There are other limitations of such short-term bioassays. For example, the combination of physical (particulate form) and chemical effects of inhaled pollutants deposited in the respiratory tract cannot be investigated using currently used short-term bioassay procedures which require that the substance tested be in dissolved form, which is very different from the form in which potentially mutagenic or carcinogenic compounds are found in airborne particles (e.g., fly ash plerospheres). Particle surfaces may also firmly bind some compounds, thus inhibiting efficient solvent extraction.

Conclusions

At least 20 metallic elements are always present in fossil fuel combustion products and their possible effects have to be considered when evaluating the carcinogenic potential of air pollution.

Trace metal compounds are contained in complex mixtures which also include a variety of organic molecules. These mixtures are embedded in a complicated mineral and/or carbonaceous matrix. The composition and structure of particulate combustion products depends on the type of fuel used,

the combustion technology and the conditions under which combustion processes are carried out.

Some trace metal compounds tend to concentrate in submicron particles of combustion products emitted into the atmosphere. Human exposure through the respiratory tract is probably the most significant exposure pathway, although in the neighborhood of large combustion facilities air pollution may also increase the intake of metal compounds through ingestion of contaminated food if such food is locally consumed.

The predictive value of whole animal bioassays carried out with single metal compounds and at large doses is low for metal compounds contained in particulate products of combustion processes.

Short-term assays represent a more promising approach to the initial evaluation of mutagenic and carcinogenic potential of air pollutants. They are less costly, less time-consuming and more suitable for testing mixtures of compounds. However, their predictive value for human carcinogenicity is limited at the present time.

The role played by metal compounds in fossil fuel combustion products cannot be evaluated with any certainty. It is not likely that they represent a major component of mutagenic and carcinogenic activity of air pollutants but they may significantly modify the effects of organic compounds which are probably the primary biologically active components.

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REFERENCES

1. Ruch, R. R., Gluskoter, H. J., and Shimp, N. F. Occurrence and Distribution of Potentially Volatile Trace Elements in Coal. Illinois Geological Survey. Environ. Geology Note 72, 1974.
2. Edwards, L. D., Muela, C. A., Sawyer, R. E., Thompson, C. M., Williams, D. H., and Delleney, R. D. Trace metals and stationary conventional combustion processes. U.S. EPA, Washington, D.C., 1981, EPA-600/S7-80-155.
3. Nicholls, G. D. The geochemistry of coal-bearing strata. In: Coal and Coal-bearing Strata, D. G. Murchison, and T. S. Westoll (Eds.), Oliver & Boyd, Ltd., Edinburgh, 1968.
4. Gluskoter, H. J. Mineral matter and trace elements in coal. In: Trace Elements in Fuels (Adv. Chem. Series 141), S. P. Babu (Ed.), American Chemical Society, Washington, DC, 1975, pp. 1-22.
5. Rao, C. P., and Gluskoter, H. J. Occurrence and Distribution of Minerals in Illinois Coals. Illinois Geological Survey Cir. 476, 1973.
6. Shah, K. R., Filby, R. H., and Haller, W. A. Determination of trace elements by neutron activation analysis. I. Determination of S, Cl, K, Ca, V, Mn, Cu, Ga and Br. J. Radioanal. Chem. 6: 185-192(1970).
7. Shah, K. R., Filby, R. H., and Haller, W. H. Determination of trace elements in petroleum by neutron activation analysis. II. Determination of Sc, Cr, Fe, Co, Ni, Zn, As, Se, Sb, Eu, Au, Hg and U. J. Radioanal. Chem. 6: 413-422(1970).
8. Williams, F. A., and Cawley, C. M. Impurities in coal and petroleum. In: The Mechanisms of Corrosion by Fuel Impurities, H. R. Johnson and D. J. Littler (Eds.), Butterworths, London, 1963.
9. American Petroleum Institute. Validation of Neutron Activation Technique for Trace Element Determination in Petroleum Products (API Publication Number 4188), American Petroleum Institute Committee on Environmental Affairs, prepared by Gulf Radiation Technology, San Diego, California, 1973.
10. Pircalabescu, I. D., and Strugaru, A. Presence of some chemical elements in the crude oil of Moreni-Gura (Romania). (in Romanian) Petrol Gaze 23: 191-198(1972).
11. Bakirova, S. F., Shestoporova, L. V., Kotova, A. V., Turkov, O. S., Benkovskii, V. G., and Aleshin, G. N. New data on trace elements composition of the ash in western Kazakhstan petroleum. Izv. Akad. Nauk Kaz. SSR, Ser. Khim. No. 4: 63-67 (1980).
12. Abu-Elgheit, M., Khalil, S. O., Barakat, A. O. Characterization of crude oils by new trace-metal indexes. Paper presented to Division of Petroleum Chemistry, American Chemical Society; Preprints 24(3): 793-797 (1979).
13. Moursy, A. S., Shalaby, A. R., M., I., and Abdou, I. K. Characteristics and trace metals of crude oil from East Belayim Feiran and Abu-Rudei's oil fields, Gulf of Suez Region. Egypt. J. Chem. 19: 451-460(1976).
14. Bertine, K. K., and Goldberg, E. D. Fossil fuel combustion and the major sedimentary cycle. Science 173: 233-235 (1971).
15. Jungers, R. H., Lee, Jr., R. E., and von Lehmden, D. J. The EPA national fuel surveillance network. I. Trace constituents in gasoline and commercial gasoline fuel additives. Environ. Health Perspect. 10: 143-150(1975).
16. Falk, H. L., and Jurgelski, Jr., W. Health effects of coal burning and combustion: carcinogenesis and cofactors. Environ. Health Perspect. 33: 203-226(1979).
17. Klein, D. H., Andren, A. W., Carter, J. A., Emery, J. F., Feldman, C., Fulkerson, W., Lyon, W. S., Ogle, J. C., Talmi, Y., Van Hook, R. I., and Bolton, N. Pathways of thirty-seven trace elements through a coal-fired power plant. Environ. Sci. Technol. 9: 973-979(1975).
18. Bencko, V., and Symon, K. Test of environmental exposure to arsenic and hearing changes in exposed children. Environ. Health Perspect. 19: 95-101 (1977).
19. Drever, I. F., Murphy, J. W., and Surdam, R. C. The distribution of As, Be, Cd, Cu, Hg, Mo, Pb and V associated with Wyodack Coal Seams Powder River Basin, Wyoming. Contrib. Geol. Univ. Wyoming, 15: 93-101(1977).
20. Paone, J. Germanium. In: Mineral Facts and Problems. U. S. Bureau of Mines Bull. No. 650, Washington, D.C., 1970, pp. 563-571.
21. Vouk, V. B. Vanadium. In: Handbook on the Toxicology of Metals, L. Friberg, G. F. Nordberg and V. B. Vouk (Eds.), Elsevier/North-Holland Biomedical Press, Amsterdam, 1979, pp. 659-685.
22. Thompson, R. J. Collection and analysis of airborne metallic elements. In: Ultratrace Metal Analysis in Biological Sciences and Environment (Adv. Chem. Ser. 172), T. H. Risby (Ed.) American Chemical Society, Washington, DC, 1979, pp. 54-72.
23. International Commission on Radiological Protection. Implication of Commission Recommendations that Doses be Kept as Low as Readily Achievable. ICRP Publication 22, Pergamon Press, Oxford, 1973.
24. Preparatory Committee of the United Nations Conference

- on the Human Environment, Third Session, 13-24 September 1971 (17/Conf. 4818), United Nations, New York, 1971, pp. 45 & 46.
25. World Health Organization. Evaluation of the Effects of Chemicals on Health. Report of a consultation on the implementation of resolution WHA 30.67, WHO, Geneva, 1978.
 26. UNEP/WHO. Report of the Meeting of a Government Expert Group on Health Related Monitoring (CEP/77.6) World Health Organization, Geneva, 1977.
 27. Nordberg, G. F., Fowler, B. A., Friberg, L., Jernelöv, A., Nelson, N., Piscator, M., Sandstead, H. H., Vostal, J., and Vouk, V. B. Factors influencing metabolism and toxicity of metals: A consensus report. *Environ. Health Perspect.*, 25: 3-41(1978).
 28. Bennett, B. G. Exposure Commitment Assessments of Environmental Pollutants. Vol. 1, No. 1, MARC Report No. 23, Monitoring and Assessment Research Center, London, 1981.
 29. Butler, G. C. (Ed.). Principles of Ecotoxicology, Scope 12, Published on behalf of the Scientific Committee on Problems of the Environment (SCOPE) by John Wiley & Sons, New York and London, 1978.
 30. Lindell, B. Dose assessment analogies. *Environ. Health Perspect.* 22: 75-78 (1978).
 31. Jones, P. Trace Metals and Other Elements in Crude Oil: Literature Review. British Petroleum Company, Sunbury, England, 1975.
 32. Lee, Jr., R. E., and von Lehmden, D. J. Trace element pollution in the environment. *J. Air Pollut. Control Assoc.* 23: 853-857(1973).
 33. Goldschmidt, V. M. The principles of distribution of chemical elements in minerals and rocks. *J. Chem. Soc.* 1937: 655-673.
 34. Bombach, J. L., Wheeler, M. A., Tabock, J., and Janowski, J. D. Distribution of contaminants in used automotive emission catalysts. *Environ. Sci. Technol.* 9: 139-143(1975).
 35. United States Tariff Commission. Synthetic Organic Chemicals. United States Production and Sales of Miscellaneous Chemicals for 1970, Washington, D. C., 1972.
 36. International Lead and Zinc Study Group. Lead in Gasoline. A Review of Current Situation. United Nations, New York, 1973: First Addendum 1974; Second Addendum, 1975; Third Addendum 1976.
 37. Moran, J. B., Manary, O. J., Fay, R. R., and Baldwin, M. J. Development of Particulate Control Techniques for Spark Ignition Engines, NTIS Report No. PB 207 312(1971).
 38. Habibi, K. Characterization of particulate matter in vehicle exhaust. *Environ. Sci. Technol.* 7: 223-234(1973).
 39. Boyer, K. W., and Laitinen, H. A. Automobile exhaust particulates. Properties of environmental significance. *Environ. Sci. Technol.* 9: 457-469(1975).
 40. Ter Haar, G. L., Lenane, D. L., Hu, J. N., and Brandt, M. Composition, size, and control of automotive exhaust particulates. *J. Air Pollut. Control Assoc.* 22: 39-46(1972).
 41. Hirschler, D. A., Gilbert, L. F., Lamb, F. N., and Niebulski, L. M. Particulate lead compounds in automobile exhaust gas. *Ind. Eng. Chem.* 49: 1131-1142(1957).
 42. Hirschler, D. A., and Gilbert, L. F. Nature of lead in automobile exhaust gas. *Arch. Environ. Health* 8: 297-313 (1964).
 43. Ninomiya, J. S., Bergman, W., and Simpson, B. H. Automotive particulate emissions. Paper presented at the 2nd International Clean Air Congress, International Union of Air Pollution Prevention Association, Washington, D. C., 1970.
 44. Ganley, J. T., and Springer, G. S. Physical and chemical characteristics of particulates in spark ignition engine exhaust. *Environ. Sci. Technol.* 8:340-347(1974).
 45. Linton, R. W., Loh, A., Natusch, D. F. S., Evans, Jr., C. A., and Williams, P. Surface predominance of trace elements in airborne particles. *Science* 191: 852-854(1976).
 46. Faggan, J. E., Bailie, J. D., Desmond, E. A., and Lenane, D. L. An evaluation of manganese as an antiknock in unleaded gasoline. Paper presented at SAE Automotive Engineering Meeting, Detroit, Mich. 1975.
 47. Ter Haar, G. I., Griffing, M. E., Brandt, M., Oberding, D. G., and Kapron, M. Methylcyclopentadienylmanganese tricarbonyl as an antiknock: composition and fate of manganese exhaust products. Paper presented at 67th Annual Meeting American Pollution Control Assoc., Denver, CO, 1974.
 48. National Academy of Sciences. Vanadium. NAS, Washington, D C, 1974.
 49. National Inventory of Sources and Emissions: Vanadium. Report prepared for the Environmental Protection Agency by W. E. Davis and Associates, Leawood, Kansas, 1971, (APTD - 1511).
 50. Bowden, A. T., Draper, P., and Rowling, H. The problem of fuel-oil ash deposition in open-cycle gas turbines. *Proc. Inst. Mech. Engr.* A167: 291-305(1953).
 51. Lee, R. E., Jr., and Duffield, F. V. Sources of environmentally important metals in the atmosphere. In: *Ultra trace Metal Analysis in Biological Sciences and Environment Adv. Chem. Ser. No. 172*, T. H. Risby (Ed.), American Chemical Society, Washington, DC, 1979, pp. 146-171.
 52. Vandegrift, A. E., Shannon, L. J., Sallee, E. E., Gorman, P. G. and Park, W. R. Particulate air pollution in the United States. *J. Air Pollut. Control Assoc.* 21: 321-328(1971).
 53. Energy Information Administration. Statistics and Trends of Energy Supply, Demand and Prices. Vol. III. Annual Report to Congress. Department of Energy, Washington, DC, DOE/EIA - 0036/3, 1977.
 54. McElroy, M. W., Carr, R. C., Ensor, D. S., and Markowski, G. R. Size distribution of fine particles from coal combustion. *Science* 215:13-19(1982).
 55. Smith, R. D. The trace element chemistry of coal during combustion and the emissions from coal-fired plants. *Prog. Energy Comb. Sci.* 6(1):53-110(1980).
 56. Abel, K. H., and Rancitelli, L. A., Major, minor, and trace elements composition of coal and flyash as determined by instrumental neutron activation analysis. In: *Trace Elements in Fuel*, Adv. Chem. Ser. 141, S. P. Babu (Ed.), American Chemical Society, Washington, DC, 1975, pp. 118-138.
 57. Zoller, W. H., Gladney, E. S., Gordon, G. E., and Bors, J. J. Emissions of trace elements from coal-fired power plants. In: *Trace Substances in Environmental Health*, Vol. VIII, D. D. Hemphill (Ed.), University of Missouri, Columbia, MO, 1974, pp. 167-171.
 58. Kaakinen, J. W., Jorden, R. M., Lawasani, M. H., and West, R. E. Trace element behavior in coal-fired power plant. *Environ. Sci. Technol.* 9: 862-869(1975).
 59. Block, C., and Dams, R. Study of flyash emission during combustion of coal. *Environ. Sci. Technol.* 10: 1011-1017(1976).
 60. Block, C., and Dams, R. Inorganic composition of Belgian coals and coal ashes. *Environ. Sci. Technol.* 9: 146-150(1975).
 61. Davison, R. L., Natusch, D. F. S., Wallace, J. R., and Evans, C. A. Trace elements in flyash. Dependence of concentration on particle size. *Environ. Sci. Technol.* 8: 1107-1113(1974).
 62. Natusch, D. F. S., Bauer, C. F., Matusiewicz, H., Evans, C. A., Baker, J., Loh, A., and Linton, R. W. Characterization of trace elements in flyash. *Proceedings International*

- Conference on Heavy Metals in the Environment, Institute of Environmental Studies, University of Toronto, Toronto, Ontario, Canada, October 27-31, 1975, pp. 553-575.
63. Schwitzgebel, K., Meserole, F. B., Oldham, R. G., Magee, R. A., and Mesich, F. G. Trace element discharge from coal-fired power plants. Proceedings International Conference on Heavy Metals in the Environment, Institute of Environmental Studies, University of Toronto, Toronto, Ontario, Canada, October 27-31, 1975, pp. 533-551.
 64. Smith, R. D., Campbell, J. A., and Nielson, K. K. Characterization and formation of submicron particles in coal-fired plants. *Atmos. Environ.* 13: 607-617(1979).
 65. Smith, R. D., Campbell, J. A., and Nielson, K. K. Concentration dependence upon particle size of volatilized elements in flyash. *Environ. Sci. Technol.* 13: 553-558(1979).
 66. Coles, D. G., Ragaini, R. C., Ondov, J. M., Fisher, G. L., Silberman, D., and Prentice, B. A. Chemical studies of stack flyash from a coal-fired power plant. *Environ. Sci. Technol.* 13: 455-459(1979).
 67. Page, A. L., Elseewi, A. A., and Straughan, I. R. Physical and chemical properties of fly ash from coal-fired power plants with reference to environmental impacts. *Residue Revs.* 71: 83-120, (1979).
 68. Swanson, V. E. Composition and trace element content of coal and power plant ash. Southwest Energy Study, Part 2, Appendix J, U. S. Geological Survey Open File Report. 1972.
 69. U. S. Environmental Protection Agency. Coal Fired Power Plant Trace Element Study, A Three Station Comparison, Vols. I and II. Reports prepared by Radian Corporation, Austin, Texas for EPA. Rocky Mountain Prairie Region, VIII. Denver, Colorado. 1975.
 70. Flagan, R. C., and Friedlander, S. K., Particle formation in pulverised coal combustion—a review. Paper presented at 82nd National Meeting, Am. Inst. Chem. Engrs., Atlantic City, N. J., August 29-Sept. 1, 1976.
 71. Natusch, D. F. S. Potentially carcinogenic species emitted to the atmosphere by fossil fueled power plants. *Environ. Health Perspect.* 22: 79-90 (1978).
 72. Collin, P. S. Some aspects of the chemistry of flyash surfaces. In: Proceedings, Symposium on the Changing Technology of Electrostatic Precipitators. Adelaide Institute of Fuel, Sydney, Australia, 1974.
 73. Dreesen, D. R., Wangen, L. E., Gladney, E. S., and Owens, J. W. Solubility of trace elements in coal fly ash. In: Environmental Chemistry and Cycling Processes, (DOE Symposium Ser. 45), D. C. Adriano, and I. L. Brisbin, Jr. (Eds.), 1978, pp. 240-252, CONF-760329.
 74. Friedlander, S. K. Smoke, Dust and Haze. Wiley-Interscience, New York, 1977.
 75. Raabe, O. G., McFarland, K. D., and Tarkington, B. K. Generation of respirable aerosols of power plant fly ash for inhalation studies with experimental animals. *Environ. Sci. Technol.* 13: 836-842 (1979).
 76. Dreesen, D. R., Wangen, L. E., Gladney, E. S., and Owens, J. W. solubility of trace elements in coal fly ash. In: Environmental Chemistry and Cycling Processes, (DOE Symposium Ser. 45), D. C. Adriano, and I. L. Brisbin, Jr. (Eds.), 1978, pp. 240-252, CONF-760329.
 77. Swaine, D. J., Trace elements in coal. In: Recent Contributions to Geochemistry and Analytical Chemistry, A. I. Tugarinov (Ed.), Wiley, New York, 1975, pp. 539-550.
 78. Ondov, J. M., Regaini, R. C., Heft, R. F., Fisher, G. L., Silberman, D., and Prentice, B. A. Interlaboratory comparison of neutron activation and atomic absorption analyses of size-classified stack fly ash. Proc. NBS 8th Materials Research Symposium on Methods and Standards for Environmental Measurement, National Bureau of Standards Gaithersburg, Md. Sept. 20-24, 1977, pp. 565-572.
 79. Danielson, J. A. Air Pollution Engineering Manual. 2nd ed., U. S. Environmental Protection Agency, Research Triangle Park, NC, Publ. No. AP-40, 1973.
 80. Vandergrift, A. E., Shannon, L. J., and Gorman, G. S. Controlling fine particles. *Chemical Engineering (Deskbook)*, 80:107-114(1973).
 81. Paulson, C. A. J., and Ramsden, A. R. Some microscopic features of fly ash particles and their significance in relation to electrostatic precipitation. *Atmos. Environ.* 4: 175-185 (1970).
 82. Ray, S. S., and Parker, F. G. Characteristics of Ash from Coal-Fired Power Plants. U. S. Environmental Protection Agency, January 1977, No. EPA-600/7-77-010.
 83. Kindersley, T. H., and Finlayson, P. C. New technology in coal combustion. In: Environmental Effects of Utilizing More Coal (Royal Society of Chemistry, Special Publication No. 37), F. A. Robinson, (Ed.), Burlington House, London, 1980, pp. 111-126.
 84. Lamb, S. I., Petrowski, C., Kaplan, I. R., and Simoneit, B. R. T. Organic compounds in urban atmospheres: a review of distribution, collection and analysis. *J. Air Pollut. Control Assoc.* 30: 1098-1115(1980).
 85. Nordberg, G. F., and Andersen, O. Metal interactions in carcinogenesis: enhancement, inhibition. *Environ. Health Perspect.* 40: 65-81(1981).
 86. Mayrsohn, I., Kuramoto, M., Crabtree, J. H., Sothorn, R. D., and Mano, H. Atmospheric Hydrocarbon Concentrations, June-September 1975. State of California Air Resources Board, Sacramento, CA, 1976.
 87. Appel, B. R., Hoffer, E. M., Haik, M., Wall, S. M., Kothny, E. L., Knights, R. L., and Wesolowski, J. J. Characterizations of Organic Particulate Matter. Final Report, July, 1977. State of California Air Resources Board Research Section, Sacramento, CA, 1977.
 88. Abeles, I. B., and Heggstad, H. E. Ethylene: an urban air pollutant. *J. Air Pollut. Control Assoc.* 23: 517-521(1973).
 89. Nassar, J., and Goldbach, J. Sources and fin variations of reactive hydrocarbon emission in the atmosphere of different industrial and rural areas. *Int. J. Environ. Anal. Chem.* 6: 145-159(1979).
 90. Grosjean, D. Secondary organic aerosols and their gas phase precursors. Paper presented at ENVR-2, 171st Meeting Am. Chem. Soc., New York, April 4-9, 1976.
 91. Pilar, S., and Graydon, N. F. Benzene and toluene distribution in Toronto atmosphere. *Environ. Sci. Technol.* 7: 628-631(1973).
 92. Santodonato, J., Howard-P., and Basu, D. Health and ecological assessment of polynuclear aromatic hydrocarbons. *J. Environ. Pathol. Toxicol.* 5: 1-364(1981).
 93. Buser, H. R. Formation and identification of tetra- and penta-chlorodibenzo-*p*-dioxins from photolysis of two isomeric hexachlorodibenzo-*p*-dioxins. *Chemosphere* 8: 251-257(1979).
 94. Buser, H. R. Formation of polychlorinated dibenzofurans (PCDF's) and debenzo-*p*-dioxins (PCDD's) from pyrolysis of chlorobenzenes. *Chemosphere* 8: 415-426(1979).
 95. Jackson, J. W. and Chang, D. P. Y. Polychlorinated biphenyl recovery from strack gas and ambient air. *J. Air Pollut. Control Assoc.* 27: 1006-1108(1977).
 96. Pomerantz, I., Burke, J., Firestone, D., McKinney, J., Roach, J. and Trotter, W. Chemistry of PCB's and PBB's. *Environ. Health Perspect.* 24: 133-146(1978).
 97. Dimitriadis, B., and Wesson, T. C. Reactivation of exhaust aldehydes. *J. Air Pollut. Control Assoc.* 22: 33-38(1972).
 98. Simoneit, B. R. T., Chester, R., and Eglinton, G. Biogenic

- lipids in particulates from lower atmosphere over the eastern Atlantic. *Nature* 267: 682-685(1977).
99. Pellizzari, E. D. Measurement of carcinogenic vapors in ambient atmospheres. Final report. Environmental Sciences Research Laboratory. Research Triangle Park, NC, 1978, EPA-600/7-78-062.
 100. Appel, B. R., Hoffer, E. M., Kothny, E. L., Wall, S. M., Haik, M., and Knights, R. L. Diurnal and spatial variations of organic aerosol constituents in the Los Angeles Basin. In: *Proceedings, Carbonaceous Particles in the Atmosphere*, T. Navakov (Ed.), NSF-LBL-9037, National Bureau of Standards, 1979, pp. 84-90.
 101. Costa, M. *Metal carcinogenesis Testing. Principles and In Vitro Methods*. The Humane Press, Clifton, NJ, 1980.
 102. International Agency for Research on Cancer. *Evaluation of the Carcinogenic Risk of Chemicals to Humans*. (IARC Monographs on the Chemicals and Industrial Processes Associated with Cancer in Humans, IARC Monographs Supplement 1), IARC, Lyon, 1979.
 103. International Agency for Research on Cancer. *Some Inorganic and Organometallic Compounds*. (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, vol. 2), IARC, Lyon, 1973, pp. 48-178.
 104. Sunderman, F. W. Metal carcinogenesis. In: *Toxicology of Trace Elements (Advances in Modern Toxicology, Vol. 2)*, R. A. Goyer, and M. A. Mehlman (Eds.), Hemisphere Publishing Corp., Washington and London, 1977, pp. 257-295.
 105. Kazantzis, G., and Lilly, L. J. Mutagenic and carcinogenic effects of metals. In: *Handbook on the Toxicology of Metals*. L. Friberg, G. F. Nordberg, and V. B. Vouk (Eds.), Elsevier/North-Holland Biomedical Press, Amsterdam, New York, 1979, pp. 237-272.
 106. *Proceedings of a Workshop/Conference in the Role of Metals in Carcinogenesis*. *Environ. Health Perspect.* 40: 1-252 (1981).
 107. Furst, A. Inorganic agents as carcinogens. In: *Environmental Cancer, (Advances in Modern Toxicology, Vol. 3)*, H. F. Kraybill, and R. A. Mehlman (Eds.), Hemisphere Publishing Corp., Washington and London/John Wiley New York-London, 1977, pp. 209-230.
 108. Furst, A. Bioassay of metals for carcinogenesis: whole animals. *Environ. Health Perspect.* 40: 83-91(1981).
 109. Leach, L. J., Yuile, C. L., Hodge, H. C., Sylvester, G. E., and Wilson, H. B. A five year inhalation study with natural uranium dioxide (UO₂) dust II. Post exposure retention and biologic effects on the monkey, dog and rat. *Health Phys.* 25: 239-255 (1973).
 110. Furst, A. Tumorigenic effect of an organic-manganese compound on F344 rats and Swiss albino mice. *J. Natl. Cancer Inst.* 60: 1171-1173(1978).
 111. Haddow, A., and Horning, E. S. On the carcinogenicity of an iron-dextran complex. *J. Natl. Cancer Inst.* 26: 109-147 (1960).
 112. Schmähli, D., and Steinhoff, D. Versuche zur Krebs-erzeugung mit kolloidalen Silber- und Goldlösungen an Ratten. *Z. Krebsforsch.* 63: 586-591(1960).
 113. Furst, H., and Haro, R. T. Carcinogenicity of metal pi-complex compounds: Metallocenes. In: *Abstracts of the 10th International Cancer Congress*, Houston, Austin, University of Texas Press, Austin, 1970, p. 28.
 114. Elinder, C. G., and Piscator, M. Zinc. In: *Handbook on the Toxicology of Metals*. L. Friberg, G. F. Nordberg and V. B. Vouk (Eds.). Elsevier/North-Holland Biomedical Press, Amsterdam-New York, 1979, pp. 675-685.
 115. Druckrey, H., Hamperl, H., and Schmähli, D. Cancerogene Wirkung von metallischen Queck-
 - silber nach intraperitonealer Gabe bei Ratten. *Z. Krebsforsch.* 61: 511-519 (1957).
 116. Bull, R. A., Van Gelder, G., Green, J. W., and Reece, W. O. Neoplastic sequelae following subcutaneous implantation of mice with rare earth metals. *Proc. Soc. Exptl. Biol. Med.* 135: 426-430(1970).
 117. Di Paolo, J. A. The potentiation of lymphosarcoma in mice by manganese chloride. *Fed. Proc.* 23: 393(1964).
 118. Roe, F. J. C., Boyland, E., and Millican, K. Effect of oral administration of two tin compounds to rats over prolonged periods. *Food Cosmet. Toxicol.* 3: 277-280(1965).
 119. Kazantzis, G. Role of cobalt, iron, lead, manganese, mercury, platinum selenium, and titanium in carcinogenesis. *Environ. Health Perspect.* 40: 143-161(1981).
 120. National Cancer Institute. *Bioassay of Selenium Sulfide (Gavage) for Possible Carcinogenicity*. U.S. Department of Health and Human Services, Washington, DC, 1980.
 121. Watt, W. D., and Kerfoot, E. J. Neoplastic effects of antimony trioxide. Paper presented at the 21 Annual Industrial Hygiene Conference, Portland, Oregon, May 28, 1981.
 122. NIOSH. Carcinogenicity and toxicity of inhaled antimony trioxide and antimony ore concentrate in rats. *Pathology Report from Experimental Pathology Laboratories*, National Institute of Occupational Safety and Health, Cincinnati, Ohio, February 1982.
 123. International Agency for Research on Cancer. *Some Metals and Metallic Compounds* (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 23), IARC, Lyon, 1980, pp. 39-415.
 124. International Agency for Research on Cancer. (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 1), IARC, Lyon, 1972, pp. 17-50.
 125. Kanisawa, M., and Schroeder, H. A. Life term studies on the effects of arsenic, germanium, tin and vanadium on spontaneous tumors in mice. *Cancer Res.* 27: 1192 (1967).
 126. Schroeder, H. A., Kanisawa, M., Frost, D. V., and Mitchener, M. Germanium, tin and arsenic in rats: Effects on growth, survival, pathological lesions and life span. *J. Nutr.* 96: 37-45(1968).
 127. Schroeder, H. A., and Mitchener, M. J. Selenium and tellurium in mice. Effects on growth, survival and tumors. *Arch. Environ. Health* 24: 66-71(1972).
 128. Schroeder, H. A., and Mitchener, M. J. Selenium and tellurium in rats: Effect on growth, survival and tumors. *J. Nutr.* 101: 1531-1540(1971).
 129. Doll, R., Fishbein, L., Infante, P., Landrigan, P., Lloyd, W. J., Mason, T. J., Mastrom Mastromatteo, E., Norseth, T., Pershagen, G., Saffiotti, U., and Saracci, R. Problems of epidemiological evidence (Proceedings of the Workshop/Conference on the Role of Metals in Carcinogenesis). *Environ. Health Perspect.* 40: 11-20(1981).
 130. Committee on the Biological Effects of Ionizing Radiation. *The Effects of Populations of Exposure to Low Levels of Ionizing Radiation*, 1980. National Academy Press, Washington, DC, 1980.
 131. Henry, M. C., Port, C. D., and Kaufman, D. G. Importance of physical properties of benzo(a)pyrene-ferric oxide mixtures in lung tumor induction. *Cancer Res.* 35: 207-213 (1975).
 132. Stenbäck, F., Sellakumar, A., and Shubik, P. Magnesium oxide on carrier dust in benzo(a)pyrene-induced lung carcinogenesis in Syrian hamsters. *J. Natl. Cancer Inst.* 54: 861-865(1975).
 133. Stenbäck, F., Rowland, J., and Sellakumar, A. Carcinogenicity of benzo(a)pyrene and dusts in the hamster lung (instilled intratracheally with titanium oxide, aluminum oxide, carbon and ferric oxide). *Oncology* 33: 29-34(1976).

134. Stenbäck, F., Ferrero, A., and Shubik, P. Synergistic effects of diethylnitrosamine and different dusts on respiratory carcinogenesis in hamsters. *Cancer Res.* 33: 2209-2214(1973).
135. Montesano, R., Saffiotti, V., Ferrero, A., and Kaufman, D. G. Synergistic effects by benzo(a)pyrene and diethylnitrosamine on respiratory carcinogenesis in hamsters. *J. Natl. Cancer. Inst.* 53: 1395-1397(1976).
136. Sunderman, F. W., J., Kasprzak, K. S., Lau, T. J., Minghetti, P. P., Maenza, R. M., Becker, N., Onkelinx, C., and Goldblatt, P. J. Effects of manganese on carcinogenicity and metabolism of nickel subsulfide. *Cancer Res.* 36: 1790-1800(1976).
137. Maenza, R. M., Pradhan, A. M., and Sunderman, F. W., Jr. Rapid induction of sarcomas in rats by combination of nickel sulfide and 3,4-benzo(a)pyrene. *Cancer Res.* 31:2067-2071(1971).
138. International Agency for Research on Cancer. Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 2), Lyon, IARC, 1980.
139. Zimmermann, F. K. Procedures used in the induction of mitotic recombination and mutation in the yeast *Saccharomyces cerevisiae*. *Mutat. Res.* 31: 71-86 (1975).
140. Hollstein, M., McCann, J., Angelosanto, F. A., and Nichols, W. W. Short-term tests for carcinogens and mutagens. *Mutat. Res.* 65: 133-226(1979).
141. Loprieno, N. Short term tests to assess the mutagenic and carcinogenic hazards of new chemicals. *Biology International* 3: 2-16(1981).
142. Hsu, T. C. (Ed.). *Cytogenetic Assays of Environmental Mutagens*. Allanheld-Osmun Publishers, Totowa, NY, 1982.
143. Belman, S., Casco, B., Flessel, C. P., Lane, B., Loeb, L., Rossman, T., Vainio, H., Whiting, R., and Zakour, R. *In vitro* models and methods for bioassay and studies of cellular mechanism. In: *Proceedings of a Workshop/Conference on The Role of Metals in Carcinogenesis*. *Environ. Health Perspect.* 40: 35-42 (1981).
144. Sirover, M. A. Effects of metals in *in vitro* bioassays. *Environ. Health Perspect.* 40: 163-172 (1981).
145. Rossman, T. G. Effects of metals on mutagenesis and DNA repair. *Environ. Health Perspect.* 40: 189-195 (1981).
146. Sunderman, Jr., W. F. Carcinogenic effects of metals. *Fed. Proc.* 37: 40-46(1978).
147. Kada, T., and Ishidate, Jr., M. *Environmental Mutagens Data Book*. Saiyontest Co., Tokyo, 1980, pp. 1.
148. Sugimura, T., Sato, S., Nago, M., Yahagi, T., Matsushima, T., Seino, Y., Takeuchi, M., and Kawachi, T. Overlapping of carcinogens and mutagens. In: *Fundamentals in Cancer Prevention (Proceedings of the 6th International Symposium of the Princess Takamatsu Cancer Research Fund, Tokyo, 1975)*, P. Magee, S. Takayama, T. Sugimura and T. Matsushima (Eds.), University Park Press, Baltimore, 1975.
149. Flessel, C. P. Metals as mutagens. In: *Inorganic and Nutritional Aspects of Cancer*, G. N. Schrauzer (ed.), Plenum Press, New York-London, 1977, pp. 117-128.
150. Vainio, H., and Sorsa, M. Chromosome aberrations and their relevance to metal carcinogenesis. *Environ. Health Perspect.* 40: 173-180(1981).
151. Zakour, R. A., Kunkel, T. A., and Loeb, L. A. Metal-induced infidelity of DNA synthesis. *Environ. Health Perspect.* 40: 197-205 (1981).
152. Nishioka, H. Mutagenic activities of metal compounds in bacteria. *Mutat. Res.* 31: 185-189 (1975).
153. Kada, T., Tutikawa, K., and Sadaie, Y. In *in vitro* and host-mediated rec-assav procedures for screening chemical mutagens; and phloxine, a mutagenic red dye detected. *Mutat. Res.* 16: 165-179 (1972).
154. Kanematsu, N., and Kada, T. Mutagenicity of metal compounds. *Mutat. Res.* 53: 207-208 (1978).
155. Sirover, M. A., and Loeb, L. A. Metal-induced infidelity during DNA synthesis. *Proc. Natl. Acad. Sci. (U.S.)* 73: 2331-2335(1976).
156. Sirover, M. A., and Loeb, L. A. Infidelity on DNA synthesis *in vitro*: screening for potential metal mutagens or carcinogens. *Science* 194:1434-1436(1976).
157. Tkeshelashvili, L. K., Shearman, C. W., Kopletz, R. M., Zakour, R. A., and Loeb, L. A. Fidelity of DNA synthesis: effects of As, Se and Cr. *Proc. Am. Assoc. Cancer Res.* 20: 263(1979).
158. Tkeshelashvili, L. K., Shearman, C. W., Zakour, R. A., Kopletz, R. M., and Loeb, L. A. Effects of arsenic, selenium and chromium on the fidelity of DNA synthesis. *Cancer Res.* 40: 2455-2460(1980).
159. DiPaolo, J. A., and Casto, B. C. Quantitative studies in *in vitro* morphological transformation of Syrian hamster cells by inorganic metal salts. *Cancer Res.* 39: 1008-1013(1979).
160. Casto, B. C., Meyers, J., and DiPaolo, J. A. Enhancement of viral transformation for evolution of the carcinogenic or mutagenic potential of inorganic metal salts. *Cancer Res.* 39: 193-198(1979).
161. Paton, G. R., and Allison, A. C. Chromosome damage in human cell cultures induced by metal salts. *Mutat. Res.* 16: 332-336(1972).
162. Umeda, M., and Nishimura, M. Inducibility of chromosomal aberrations by metal compounds in cultured mammalian cells. *Mutat. Res.* 67: 221-229(1979).
163. Kada, T., Hirano, K., and Shirasu, Y. Screening of environmental mutagens by rec-assay system with *Bacillus subtilis*. In: *Chemical Mutagens, Principles and Methods for Their Detection*, Vol. 6. F. J. de Serres, and A. Hollaender (Eds.), Plenum Press, New York and London, 1980, pp. 149-173.
164. Deknuddt, G., and Deminatti, M. Chromosome studies in human lymphocytes after *in vitro* exposure to metal salts. *Toxicology* 10: 67-76(1978).
165. Léonard, A., and Lauwerys, R. R. Carcinogenicity, teratogenicity and mutagenicity of arsenic. *Mutat. Res.* 75: 49-62(1980).
166. Kuschner, G. The carcinogenicity of beryllium. *Environ. Health Perspect.* 40: 101-105(1981).
167. International Agency for Research on Cancer. Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals, and General Considerations on Volatile Anaesthetics (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 11) IARC, Lyon, 1976, pp. 39-112.
168. Degraeve, N. Carcinogenic, teratogenic and mutagenic effects of cadmium. *Mutat. Res.* 86: 115-135(1981).
169. Norseth, T. The carcinogenicity of chromium. *Environ. Health Perspect.* 40: 121-130(1981).
170. Léonard, A., and Lauwerys, R. R. Carcinogenicity and mutagenicity of chromium. *Mutat. Res.* 76: 227-239(1980).
171. Gerber, G. B., Léonard, A., and Jacquet, P. Toxicity, mutagenicity and teratogenicity of lead. *Mutat. Res.* 76: 115-141(1980).
172. Sunderman, Jr., F. W. Recent research on nickel carcinogenesis. *Environ. Health Perspect.* 40: 131-141(1981).
173. Léonard, A., Gerber, G. B., and Jacquet, P. Carcinogenicity and teratogenicity of nickel. *Mutat. Res.* 87: 1-15(1981).
174. Waksvik, H., Bayseen, M., Broegger, A., Saxholm, H., and Reith, A. *In Vivo* and *in vitro* studies of mutagenicity and carcinogenicity of nickel compounds in man. Poster presented at 10th Annual Meeting EEMS, Athens, Post 32

- (1980).
175. Kanematsu, N., Hara, M., and Kada, T. The assay and mutagenicity studies on metal compounds. *Mutat. Res.* 77: 109-116 (1980).
176. Nakamuro, K., Yoshikawa, K., Sayato, Y., and Kurata, H. Comparative studies of chromosomal aberration and mutagenicity of trivalent and hexavalent chromium. *Mutat. Res.* 58: 175-181(1978).
177. Nestmann, E. R., Matula, T. I., Douglas, G. R., Bora, K. C., and Kowbell, D. J. Detection of the mutagenic activity of lead chromate using a battery of microbial tests. *Mutat. Res.* 66: 357-365 (1979).
178. Rosenkrantz, H. S., and Poirier, L. A. Evaluation of the mutagenicity and DNA - modifying activity of carcinogens and non-carcinogens in microbial systems. *J. Natl. Cancer Inst.* 62: 873-892(1972).
179. Lo, L. W., Koropatnick, J., and Stich, H. I. The mutagenicity and cytotoxicity of selenite, "activated" selenite and selenate for normal and DNA repair-deficient human fibroblasts. *Mutat. Res.* 49: 305-312(1978).
180. Loeb, L. A., Sirover, M. A., Weymouth, L. A., Dube, D. K., Seal, G., Agarwal, S., and Katz, E. Infidelity of DNA synthesis as related to mutagenesis. *J. Toxicol. Environ. Health*, 2: 1297-1304(1977).
181. Loeb, L. A., Sirover, M. A., and Agarwal, S. A. Infidelity of DNA Synthesis as related to mutagenesis and carcinogenesis. In: *Inorganic and Nutritional Aspects of Cancer*, G. N. Schrauzer (Ed.), Plenum Press, New York-London, 1977, pp. 103-115.
182. Loeb, L. A., and Zakour, R. A. Metals and genetic miscoding. In: *Nucleic Acid Metal Ion Interactions*, T. G. Spiro (Ed.), John Wiley New York, 1980, pp. 117-144.
183. Miyaki, M., Akamatsu, N., Suzuki, K., Araki, M., and Ono, T. Quantitative and Qualitative Changes Induced in DNA Polymerases by Carcinogens. In: *Genetic and Environmental Factors in Experimental and Human Cancer*, H. V. Gelboin, B. MacMahon, T. Metsushima, T. Sugimura, S. Takayama, and H. Takebe (Eds.), Japan Sci. Soc., Press, Tokyo, 1980, pp. 201-213.
184. Seal, G., Sherman, C. W., and Loeb, L. A. On the fidelity of DNA replication. Studies with human placenta DNA polymerases. *J. Biol. Chem.* 254: 5229-5237 (1979).
185. Brusick, D., Gletten, F., Japannath, O., and Weeke, V. The mutagenic activity of ferrous sulfate for *Salmonella typhimurium*. *Mutat. Res.* 38: 380-381 (1976).
186. Kalinina, L. M., Poluhina, G. N., and Lukaseva, L. I. *Salmonella typhimurium* test system for indication of mutagenic activity of environmental hazards. I. Detection of mutagenic effect heavy metal salts using *in vivo* and *in vitro* assays without metabolic activation. *Genetika*, 13: 1089-1092(1977).
187. Löfroth, G., and Ames, B. N. Mutagenicity of inorganic compounds in *Salmonella typhimurium*: arsenic, chromium and selenium. *Mutat. Res.* 53:65-66(1978).
188. Petrilli, F. L., and DeFlora, S. Toxicity and mutagenicity of hexavalent chromium on *Salmonella typhimurium*. *Appl. Environ. Microbiol.* 33: 805-809(1977).
189. Petrilli, F. L., and DeFlora, S. Metabolic deactivation of hexavalent chromium mutagenicity. *Mutat. Res.* 54: 139-147(1978).
190. Petrilli, F. L., and DeFlora, S. Oxidation of inactive trivalent chromium to the mutagenic hexavalent form. *Mutat. Res.* 58: 167-173(1978).
191. Simmon, V. F. *In vitro* mutagenicity assays of chemical carcinogens and related compounds with *Salmonella typhimurium*. *J. Natl. Cancer Inst.* 62: 893-899(1979).
192. Tamaro, M., Venturini, S., Eftimiadi, C., and Monti-Bragadin, C. Interaction of platinum compounds with bacterial DNA. *Experientia*, 33:337-319(1977).
193. Tamaro, M., Venturini, S., Monti-Bragadin, C., Saincich, G. Mestroni, G., and Zassinovich, G. Effects in bacterial systems of Pt(II) complexes with antitumour activity. *Chem. Biol. Interact.* 26: 179-184(1979).
194. Tindall, K. R., Warren, G. R., and Skaar, P. D. Metal ion effects in microbial systems. *Mutat. Res.* 53: 90-91(1978).
195. Poluhina, G. N., Kalinina, L. M. and Lukaseva, L. I. *Salmonella typhimurium* test system for indication of mutagenic activity of environmental hazards. II. Detection of mutagenic effect of heavy metal salts using *in vitro* assay with metabolic activation. *Genetika*, 13: 1492-1496(1977).
196. Hemmerly, J., and Demerec, M. Tests of chemicals for mutagenicity. *Cancer Res.* 15(Suppl. 3): 68-75(1955).
197. Ishizawa, M. *Escherichia coli* WP2 strain. Hen'igen to Dokusei 8:29-36 (1979).
198. Venitt, S., and Levy, L. Mutagenicity of chromates in bacterial cells and its relevance to chromate carcinogenesis. *Nature* 20: 493-495(1974).
199. Green, M. H. L., Muriel, W. J., and Bridges, B. A. Use of a simplified fluctuation test to detect low levels of mutagens. *Mutat. Res.* 38: 33-62 (1976).
200. Speck, W. I., Santanella, R. M., and Rosenkrantz, H. S. An evaluation of the prophase i induction test (inductest) for the detection of potential carcinogens. *Mutat. Res.* 54: 101-104(1978).
201. DiPaolo, J. A., Nelson, R. L., and Casto, B. C. *In vitro* neoplastic transformation of Syrian hamster cells by lead acetate and its relevance to environmental carcinogenesis. *Brit. J. Cancer* 38: 452-655(1978).
202. Pienta, R. J., Pooley, J. A., and Lebherz, III, W. B. Morphological transformation of early passage golden Syrian hamster embryo cells derived from myopreserved primary cultures as a reliable *in vitro* bioassay for identifying diverse carcinogens. *Int. J. Cancer*, 19: 642-655(1977).
203. Rivedal, E., and Sanner, T. Metal salts as promoters of *in vitro* morphological transformation of hamster embryo cells initiated by benzo(a)pyrene. *Cancer Res.* 41: 2950-2953(1981).
204. Baranowska, H., Ejchart, A., and Putrament, A. Manganese mutagenesis in yeast. V. On mutation and conversion induction in nuclear DNA. *Mutat. Res.* 42: 343-347 (1977).
205. Putrament, A., Baranowska, H., Ejchart, A., and Jachywczyk, R. Manganese mutagenesis in yeast. VI. Mn^{2+} uptake, mitDNA replication and E^+ induction. Comparison with other divalent cations. *Molec. Gen. Genet.* 151: 69-76(1977).
206. Simmon, V. F. *In vitro* assays for recombinogenic activity of chemical carcinogens and related compounds with *Sacharomyces cerevisiae* D3. *J. Natl. Cancer Inst.*, 62: 901-909 (1979).
207. Bonatti, S., Meini, M., and Abbodandolo, A. Genetic effects of potassium dichromate in *Schizosacharomyces pombe*. *Mutat. Res.* 38:147-150(1976).
208. Beek, B., and Obe, G. Effect of lead acetate on human leukocyte chromosomes *in vitro*. *Experientia*, 30: 1006-1007(1974).
209. Beek, B., and Obe, G. The human leukocyte test system. VI. The use of sister chromatid exchanges as possible indicators for mutagenic activities. *Humangenetik*, 29: 127-134(1975).
210. MacRae, W. D., Whitney, R. F., and Stich, H. F. Sister chromatide exchanges induced in cultured mammalian cells by chromate. *Chem. Biol. Interact.* 26: 281-286(1979).
211. Nakamuro, K., Yoshikawa, K., Sayato, Y., Kurata, U., Tonomura, M., and Tonomura, A. Studies on selenium-related compounds. V. Cytogenetic effect and reactivity with DNA. *Mutat. Res.* 40:177-184(1976).
212. Newman, S., Summitt, R. L., and Nunez, L. J. Incidence of nickel induced sister chromatid exchange. *Mutat. Res.*

- 101: 67-75(1982).
213. Oppenheim, J. P., and Fishbein, W. N. Induction of chromosome breaks in cultured normal human leukocytes by potassium arsenite, hydroxyurea and related compounds. *Cancer Res.* 25: 980-985(1975).
214. Petres, J., and Hundelker, M. "Chromosome pulverisation" induced *in vitro* in cell cultures by arsenic. *Arch. Klin. Exp. Dermatol* 231: 366-370 (1968).
215. Stella, H., Montaldi, A., Rossi, R., Rossi, G., and Levis, A. G. Clastogenic effects of chromium on human lymphocytes *in vitro* and *in vivo*. *Mutat. Res.* 101: 151-164(1982).
216. Wulf, H. C. Sister chromatid exchanges in human lymphocytes exposed to nickel and lead. *Dan. Med. Bull.* 27: 40-42(1980).
217. Bauchinger, M., and Schmid, E. Chromosomenanalysen in Zellkulturen des Chinesischen Hamsters nach Applikation von Bleiacetat. *Mutat. Res.* 14: 95-100(1972).
218. Levis, A. G., and Majone, F. Cytotoxic and clastogenic effects of soluble chromium compounds on mammalian cell cultures. *Brit. J. Cancer* 40: 523-533 (1979).
219. Majone, F., and Levis, A. G. Chromosomal aberrations and sister-chromatid exchanges in Chinese hamster cells treated *in vitro* with hexavalent chromium compounds. *Mutat. Res.* 67: 231-238(1979).
220. Newbold, R. F., Amos, J., and Connell, J. R. The cytotoxic, mutagenic and clastogenic effects of chromium containing compounds on mammalian cells in culture. *Mutat. Res.* 67: 55-63(1979).
221. Ohno, H., Hanaoka, F., and Yamada, M. Inductability of sister chromatid exchanges by heavy metal ions. *Mutat. Res.* 104: 141-145(1982).
222. Röhr, G., and Bauchinger, M., Chromosome analyses in cell cultures of the Chinese hamster after application of cadmium sulfate. *Mutat. Res.* 40: 125-130(1976).
223. Tsuda, H. and Kato, K. Chromosomal aberrations and morphological transformation in hamster embryonic cells treated with potassium dichromate *in vitro*. *Mutat. Res.* 46: 87-96(1977).
224. Bigaliev, A. B., Turebaev, M. N., Bigalieva, R. K., and Elemesova, M. Sh. Cytogenetic examination of people engaged in chromium production. *Genetika*, 13: 545-547(1977).
225. Bijlsma, J. B., and deFrance, H. F. Cytogenetic investigation in volunteers ingesting inorganic lead. *Int. Arch. Occup. Environ. Health* 38: 145-148(1976).
226. Deknadt, G., Manuel, U., and Gerber, G. B. Chromosomal aberrations in workers professionally exposed to lead. *J. Toxicol. Environ. Health* 3: 885-891(1977).
227. Forni, A., Cambiaghi, G., and Secchi, G. C. Initial occupational exposure to lead: chromosome and biochemical findings. *Arch. Environ. Health* 31: 73-75(1976).
228. Högstädt, B., Kolnig, A.-M., Mitelman, F., and Schütz, A. Correlation between blood-lead and chromosomal aberrations. *Lancet* 2: 262(1979).
229. Nordenson, J., Beckman, G., Beckman, L., and Nordström, S. Occupational and environmental risks in and around a smelter in northern Sweden. II. Chromosomal aberrations in workers exposed to arsenic. *Hereditas* 88:47-50 (1978).
230. Nordenson, I., Salmonsson, S., Brun, E., and Beckman, G. Chromosome aberrations in psoriatic patients treated with arsenic. *Human Genet.* 48:1-6(1979).
231. O'Riordan, M. L., and Evans, H. J. Absence of significant chromosome damage in males occupationally exposed to lead. *Nature* 247: 50-53(1974).
232. O'Riordan, M. L., Hughes, E. G., and Evans, H. J. Chromosome studies on blood lymphocytes of men occupationally exposed to cadmium. *Mutat. Res.* 58:305-311(1978).
233. Petres, J., Schmid-Ulrich, K., and Wolf, V. Chromosomenaberrationen am menschlichen Lymphocyten bei chemischen Arsenschäden, *Deut. Med. Wschr.* 2: 79-80(1970).
234. Nashed, N. Preparation of peritoneal cell metaphases of rats, mice, and Chinese hamsters cells after mitogenic stimulation with magnesium sulfate and/or aluminum hydroxide. *Mutat. Res.* 30: 407-416(1975).
235. Watanabe, M., Honda, S., Hayashi, M., and Matsuda, T. Mutagenic effects of combinations of chemical carcinogens and environmental pollutants in mice as shown by the micronucleus test. *Mutat. Res.* 97: 43-48(1982).
236. Wild, D. Cytogenetic effects in the mouse of 17 chemical mutagens and carcinogens evaluated by the micronuclear test. *Mutat. Res.* 56: 319-327(1978).
237. Harnden, D. G. Relevance of short-term carcinogenicity tests to the study of the carcinogenic potential of urban air. *Environ. Health Perspect.* 22: 67-70(1978).
238. Drake, J. W., de Serres, F. J., Darby, N. J., Dunkel, V. C., Longfellow, D. G. Ott, H. Purchase, I. F. H., Ramel, C., Schlatter, C., and Smith, E. M. B. Rationale for deployment of short-term assays for evidence of carcinogenicity. In: Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal (IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans, Supplement 2), Lyon, IARC, 1980, pp. 295-308.
239. World Health Organization. Environmental Health Criteria 6: Principles and Methods for Evaluating the Toxicity of Chemicals, Part I, p. 263, Geneva, WHO, 1978, p. 236-264.
240. Chrisp, C. E., and Fisher, G. L. Mutagenicity of airborne particles, *Mutat. Res.* 76: 143-164(1980).
241. Daisey, J. M., Kneip, T. J., Hawryluk, I., and Mukai, F. Seasonal variations in the bacterial mutagenicity of airborne particulate organic matter in New York City. *J. Am. Chem. Soc.* 102: 1487-1490(1980).
242. Hedenstedt, A., Jenssen, D., Lidesten, B.-M., Ramel, C., Rannug, V., and Stern R. M. Mutagenicity of fume particles from stainless steel welding. *Scand. J. Work Environ. Health*, 3: 203-211(1977).
243. Maxild, J., Andersen, M. Kiel, P., and Stern, K. M. Mutagenicity of fume particles from metal arc welding on stainless steel in the *Salmonella*/microsome test. *Mutat. Res.* 56:235(1978).
244. Commoner, B., Madyastha, P., Bronsdon, A., and Vithayathil, A. J. Environmental mutagens in urban air particulates. *J. Toxicol. Environ. Health*, 4: 59-77(1978).
245. Pitts, Jr., J. N., van Cauwenberghe, K. A., Grosjean, D., Schmid, J. P., Fritz, D. R., Belsen, Jr., W. L., Knudson, G. B., and Hynds, P. M. Atmospheric reactions of polycyclic aromatic hydrocarbons: facile formation of mutagenic nitro derivatives. *Science* 202: 515-519(1978).
246. Fisher, G. L., and Chrisp, C. E. Physical and biological studies of coal fly ash. In: Application of Short-Term Bioassays in the Fractionation and Analysis of Complex Environmental Mixtures, M. D. Waters, S. Nesnow, J. L. Huisinigh, S. S. Sandhu, and L. Claxton (Eds.), Plenum Press, New York, 1979, pp. 443-461.
247. Fisher, G. L., Chrisp, C. E., and Raabe, O. G. Physical factors affecting the mutagenicity of fly ash from a coal-fired power plant. *Science* 204: 879-881(1979).
248. Fisher, G. L., Chang, D. P. Y., and Brummer, M. Fly ash collected from electrostatic precipitation: Microcrystalline structure and the mystery of spheres. *Science*, 192: 553-555 (1976).
249. Teranishi, K., Hamiada, K., and Watanabe, H. Mutagenicity in *Salmonella typhimurium* mutants of the benzene-soluble organic matter derived from airborne particulate matter and its five fractions. *Mutat. Res.* 56: 273-280 (1978).